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Original Contribution

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1—Full Report

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Abstract: The leadership of the National Lipid Association convened an Expert Panel to develop a consensus set of recommendations for patient-centered management of dyslipidemia in clinical medicine. An Executive Summary of those recommendations was previously published. This document provides support for the recommendations outlined in the Executive Summary. The major conclusions include (1) an elevated level of cholesterol carried by circulating apolipoprotein B-containing lipoproteins (non–high-density lipoprotein cholesterol 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. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies; (3) the intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event; (4) atherosclerosis is a process that often begins early in life and progresses for decades before resulting a clinical ASCVD event. Therefore, both intermediate-term and long-term or 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) nonlipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus; and (7) the measurement and monitoring of atherogenic cholesterol levels remain an important part of a comprehensive ASCVD prevention strategy. © 2015 National Lipid Association. All rights reserved.

Various organizations and agencies have issued recommendations for the management of dyslipidemia.[3–11] Although many commonalities exist among them, material differences are present as well. The leadership of the National Lipid Association (NLA) convened an Expert Panel to develop a consensus set of recommendations for patient-centered management of dyslipidemia in clinical medicine. A presentation containing the main elements of these recommendations was made available to the public and other organizations involved with the prevention of atherosclerotic cardiovascular disease (ASCVD) to solicit input during an open comment period. Comments and suggestions were received from many members of the NLA, as well as other individuals and organizations, and were collated for consideration and adjudication by the panel in formulating the final set of recommendations contained herein.[12] The NLA Expert Panel graded the type and strength of the evidence supporting their recommendations using a hybrid of the rating system developed by the National Heart, Lung, and Blood Institute's Evidence-Based Methodology Lead and adapted from the original GRADE system of evidence rating.[1–3,13]

Part 1 of the NLA Expert Panel recommendations for patient-centered management of dyslipidemia covers the following:

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

- Screening and classification of lipoprotein lipid levels in adults (>20 years);
- Targets for intervention in dyslipidemia management;
- ASCVD risk assessment and treatment goals based on risk category;
- Atherogenic cholesterol—non–high-density lipoprotein (non-HDL) cholesterol (non-HDL-C) and low-density lipoprotein (LDL) cholesterol (LDL-C)—as the primary targets of therapy; and
- Lifestyle and drug therapies intended to reduce morbidity and mortality associated with dyslipidemia.

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

- Lifestyle therapies (to provide a greater depth of information than is included in part 1);
- Groups with special considerations:
  - Children and adolescents;
  - Gender, including pregnancy;
  - Ethnic groups;
  - Older patients;
  - Patients with human immunodeficiency virus;
  - Patients with selected chronic inflammatory states;
  - Patients with residual risk despite statin therapy;
- Strategies to assist with patient adherence; and
- Team-based collaborative care.

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

Taken from Jacobson et al.[1] Originally published in James et al.[2] and Stone et al.[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 the new American Heart Association/American College of Cardiology cholesterol guidelines[3] and adapted from the original GRADE system of evidence rating.[13]

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

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.[2]

Taken from Jacobson et al.[1] Originally published in James et al.[2] and Stone et al.[3]

*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. Additional details regarding the evidence quality rating system are available in the online Supplement.

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

Clinical decisions often need to be made in the absence of ideal or complete evidence, and well-informed experts will not always evaluate or interpret the evidence base in the same way. Clinical recommendations aim to assist clinicians in making decisions about the best strategies for management of a condition, taking into account potential benefits and risks of the available options. The NLA Expert Panel recommendations are intended to inform, not replace, clinical judgment. A patient-centered approach dictates that clinical judgment take into account the circumstances, objectives, and preferences of each individual patient.[3,14,15] The patient should be an active participant in the process, having engaged with the clinician in a dialog about the objectives of therapy, including potential risks and side effects, as well as benefits and costs. Patient-provider collaboration in treatment decisions tends to improve long-term adherence.[16–18]

The NLA recognizes the major contribution that dyslipidemia management has made to the progressive reduction in ASCVD morbidity and mortality that has been observed during recent decades (Fig. 1).[19] This reduction in risk

occurred under the guidance provided by previous guidelines and recommendations, most notably the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) Guidelines.[4,20] The NLA Expert Panel consensus view is that the evidence that has accumulated since the 2004 update of the NCEP ATP III guidelines warrants a modest refinement of previous lipid-related risk management strategies, as outlined in the present report.

The evidence base considered in the development of consensus for these recommendations emphasized results from randomized controlled trials (RCTs) to evaluate lipid-altering interventions on clinical ASCVD events (mainly myocardial infarction, coronary death, and stroke), including subgroup assessments and pooled analyses from multiple trials, where available. Although the panel acknowledges that the primary results from RCTs represent the strongest evidence from which to draw conclusions about benefits and risks of treatment strategies, it also recognizes that many important clinical questions have not been addressed in RCTs (hence the evidence base is incomplete), and RCT evidence may have uncertain relevance to particular patients because the RCTs were performed in highly selected groups with characteristics that may differ in important ways from the patient for whom treatment decisions need to be made.
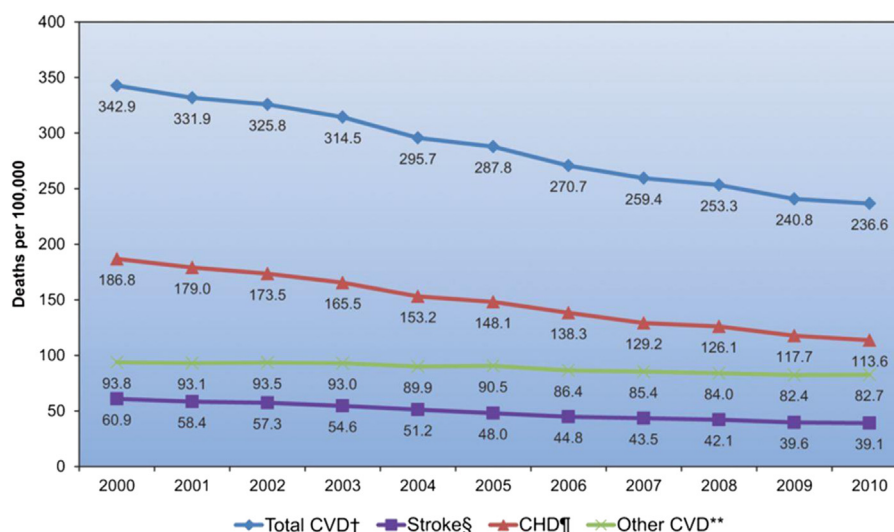
Figure 1 US age-standardized death rates attributable to CVD, 2000 to 2010.[19] Taken from Go AS et al.[19] with permission. CHD, coronary heart disease; CVD, cardiovascular disease. †Total CVD: International Classification of Diseases, 10th Revision (ICD-10) from I00 to I99 and from Q20 to Q28. §Stroke (all cerebrovascular disease): ICD-10 from I60 to I69. ¶CHD: ICD-10 from I20 to I25. **Other CVD: ICD-10 from I00 to I15, from I26 to I51, from I70 to I78, from I80 to I89, and from I95 to I99.

Observational evidence from epidemiologic studies is subject to possible bias and confounding and is therefore sometimes excluded from deliberations regarding treatment recommendations.[3] However, where the available observational evidence is of high quality, with consistent results across investigations in multiple cohorts by different investigators, such evidence can play an important role to inform clinical investigations. Genetic epidemiologic studies, because they examine genetic variants that often produce lifelong differences in levels of lipoprotein lipid concentrations, overcome many of the difficulties with the potential for bias and confounding inherent in other observational studies. Therefore, in addition to data from RCTs, evidence from epidemiologic and genetic studies as well as metabolic and mechanistic investigations has been considered in the development of these recommendations. This approach allowed inclusion of a broad evidence base for clinical decision making and was consistent with the approach taken by the NCEP ATP III and many other international recommendations committees.[5,7,8,21]

Major conclusions of the NLA Expert Panel

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

1. An elevated level of cholesterol carried by circulating apolipoprotein (apo) B–containing lipoproteins (non–HDL-C and LDL-C, termed atherogenic cholesterol) is a root cause of atherosclerosis, the key underlying process contributing to most clinical ASCVD events.

HDL, LDL, intermediate-density lipoprotein (IDL), very low–density lipoprotein (VLDL), and chylomicrons are the 5 major classes of lipoproteins. Of these, LDL is the predominant cholesterol-carrying lipoprotein comprising ∼75% of cholesterol carried by non-HDL particles, with the remaining ∼25% of non–HDL-C in triglyceride-rich particles, which include VLDL, IDL, chylomicrons, and their remnants.[22–28] Each LDL particle contains a single apo B100 particle, whereas the major apos of VLDL are apo B100, apo A4, apo C (1, 2, and 3), and apo E. Chylomicron particles contain the same apos as VLDL, except that they also contain apo A (1, 2, and 4), and apo B48 is present instead of apo B100. It should be noted that clinical laboratories typically report the LDL-C concentration as a calculated value using the Friedewald equation (LDL-C = total cholesterol [total-C] – HDL-C – triglycerides/5 with all values in mg/dL) as long as the triglyceride level is below ∼400 mg/dL.[29] This calculated value includes cholesterol carried by true LDL particles, as well as IDL particles. Also, some particles, mostly in the LDL density range, are covalently bound to apolipoprotein (a). LDL-C estimated by the Friedwald equation also includes cholesterol carried by these lipoprotein (a) [Lp (a)] particles.

Non–HDL-C (calculated as total-C – HDL-C) represents the sum of cholesterol carried by all potentially atherogenic, apo B-containing lipoprotein particles, including LDL, IDL, Lp (a), VLDL (including VLDL remnants), and chylomicron particles and remnants. The NCEP ATP III acknowledged the importance of non–HDL-C in atherogenesis in 2002, but, at that time, instructions to target non–HDL-C concentration pertained only to individuals with hypertriglyceridemia because it was understood that elevated levels of VLDL cholesterol (VLDL-C) and its remnants are more prevalent in those with hypertriglyceridemia.[4,30] However, a substantial body of evidence has since accumulated to support the view that non–HDL-C is more strongly related to risk for ASCVD than LDL-C
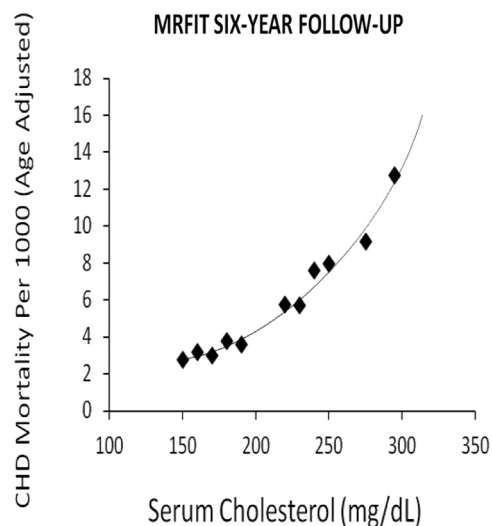
Figure 2   Log-linear relationship between serum cholesterol and coronary heart disease (CHD) mortality from the Multiple Risk Factor Intervention Trial (N = 356,222).[8,50]

smooth muscle proliferation. The proliferation of smooth muscle cells creates a fibrous cap or plaque.[43] As the plaque matures and atherogenic particles continue to infiltrate, lipid-rich areas form within the fibrous plaque.[41] Inflammation triggers processes that weaken the fibrous cap and make the plaque susceptible to rupture.[44] Thus, atherogenic lipoproteins play important roles in the initiation of atherosclerosis, progression to a mature plaque and, eventually, plaque instability and rupture. When plaque rupture occurs, subendothelial components are exposed to the blood, and luminal thrombosis occurs, which, if sufficiently large, can occlude arterial flow. Atherosclerotic plaque rupture is generally the proximal cause of acute coronary syndromes (eg, myocardial infarction, unstable angina).[45–48]

Epidemiologic studies have demonstrated a strong relationship between serum cholesterol levels and increased ASCVD risk, and, conversely, low rates of ASCVD are associated with low levels of cholesterol (Fig. 2).[49–53] The importance of LDL-C in ASCVD is corroborated by the existence of familial hypercholesterolemia (FH), an autosomal codominant genetic disorder characterized by very high levels of LDL-C (and LDL particles) and early ASCVD.[54,55] In patients with FH, the removal of apo B–containing lipoproteins by lipoprotein apheresis has been shown to markedly reduce arterial wall inflammation.[41] Individuals with proprotein convertase subtilisin kexin type 9 (PCSK9) mutations and with polymorphisms in Niemann-Pick C1-like 1 (NPC1L1) protein that result in reduced levels of LDL-C throughout life are associated with markedly reduced risk for ASCVD events.[56–58]

A causal relationship between triglyceride-rich lipoprotein cholesterol levels (sometimes referred to as "remnant cholesterol" [calculated as total-C – HDL-C – LDL-C]) is supported by an association between elevated triglycerides and increased ASCVD risk,[59–64] as well as by the high risk for ASCVD among individuals with atherogenic dyslipidemia (combination of elevated triglycerides and low
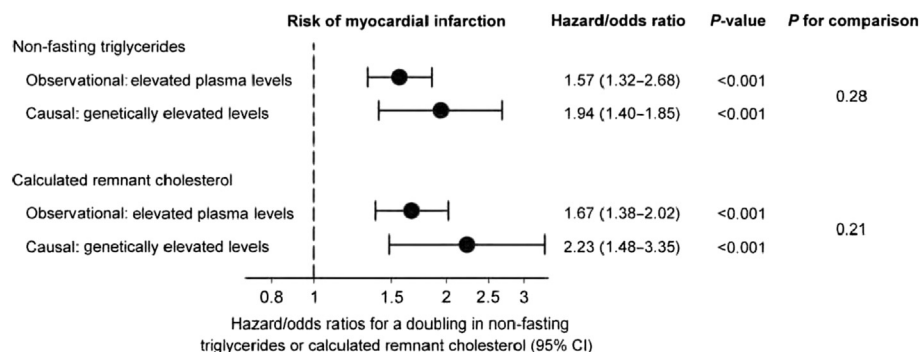
and that this relationship is evident in those with and without hypertriglyceridemia.[31–37]

Atherosclerosis has been described as a lipid-driven inflammatory disorder of the arterial wall.[38–41] Atherogenic lipoproteins (LDL and some smaller species of the triglyceride-rich lipoproteins) have the ability to infiltrate the arterial wall thereby initiating atherosclerosis. After entering the arterial wall, the particles bind to proretentive extracellular molecules, become trapped, and are modified through oxidation and other processes, which increase their inflammatory properties and their unregulated uptake by macrophages.[40,42] As the macrophages become engorged with lipid, they form foam cells, and this process triggers a potentiation of the inflammatory response through release of compounds that increase recruitment of additional monocytes and macrophages. The accumulation of foam cells leads to the development of a fatty streak that initiates

Figure 3   Association between elevated triglycerides and remnant cholesterol and risk of myocardial infarction.[67] The observational risk estimates for a doubling in nonfasting triglycerides or calculated remnant cholesterol are from the Copenhagen City Heart Study as hazard ratios. The causal risk estimates for a doubling in nonfasting triglycerides or calculated remnant cholesterol levels are for the combined genotypes (c.-3A>G, S19W, and c.*31C>T genotypes) in the Copenhagen General Population Study, the Copenhagen City Heart Study and the Copenhagen Ischemic Heart Disease studies combined (n = 60,113). Adjustment was for age, sex, smoking, hypertension, and diabetes mellitus. P values are for significance of risk estimates, and P values for comparison are for differences between observational and causal genetic risk estimates. Taken from Jorgensen AB et al.[67] with permission of Oxford University Press. CI, confidence interval.
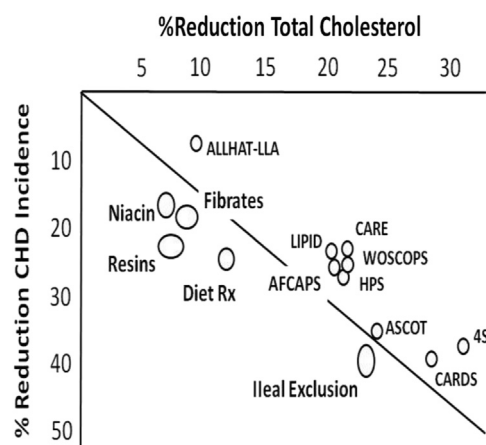
Figure 4 Relationship between percent reduction in total cholesterol and percent reduction in coronary heart disease (CHD) incidence.[8]

HDL-C).[64] Genetic mutations that result in increased circulating levels of triglycerides and triglyceride-rich lipoprotein cholesterol (eg, variants associated with lipoprotein lipase, apo C3, and apo A5) are associated with elevated ASCVD risk (Fig. 3).[27,28,62,65–69]

As discussed in more detail in the following, RCTs of lipid-altering interventions that lower levels of LDL-C and/or triglyceride-rich lipoprotein cholesterol levels have demonstrated reduced ASCVD event risk, further supporting a causal role of apo B–containing lipoproteins in the atherothrombotic process. The relative importance of lowering atherogenic particle concentrations vs the levels of cholesterol carried by atherogenic particles is incompletely understood. Non–HDL-C has been regularly shown

to be a better predictor of ASCVD event risk than LDL-C, which may, at least in part, reflect the stronger relationship between the non–HDL-C concentration and circulating levels of atherogenic particles.[70] Thus, the panel included both LDL-C and triglyceride-rich lipoprotein cholesterol (non–HDL-C is the sum of LDL-C and triglyceride-rich lipoprotein cholesterol) as atherogenic cholesterol components.

2. Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies.

Numerous clinical trials of atherogenic cholesterol–lowering therapies have demonstrated their ability to reduce the incidence of ASCVD in proportion to the amount of LDL-C and non–HDL-C reduction (Fig. 4).[4,8,37,71,72] Examinations of on-treatment LDL-C concentration compared with coronary heart disease (CHD) events in studies of primary prevention (ie, in subjects initially free from CHD; Fig. 5)[73–76] and in studies of secondary prevention (ie, in patients with established ASCVD; Fig. 6)[8,77–83] also show a strong positive correlation. These effects are evident not only with atherogenic cholesterol–lowering drug therapies but also diet/lifestyle and surgical therapies.[4,8,20,71–96] Furthermore, the relationship is present across the full spectrum of LDL-C and non–HDL-C levels (Fig. 7).[8,37,92,97] The Cholesterol Treatment Trialists' meta-analysis of more- vs less-intensive statin regimens demonstrated that a 1.0 mmol/L (38.7 mg/dL) change in LDL-C resulted in a 22% relative risk reduction (hazard
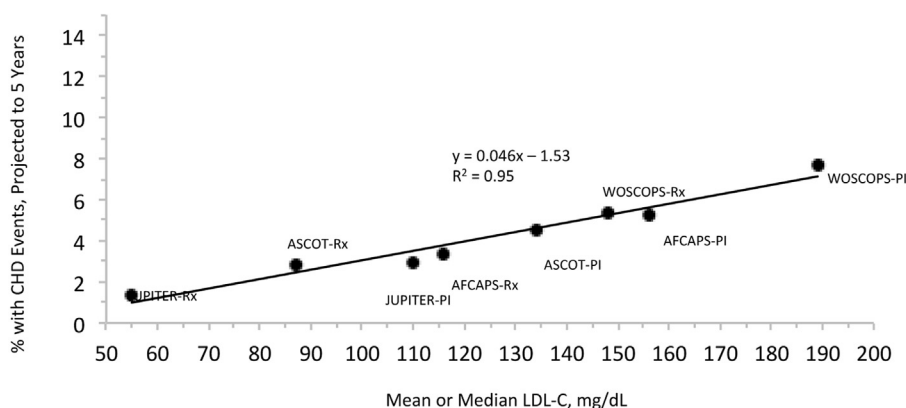
Figure 5 Relationship between on-treatment low-density lipoprotein cholesterol (LDL-C) concentration and coronary heart disease (CHD) events in studies of primary prevention.[73–76] Pl, placebo; Rx, treatment.
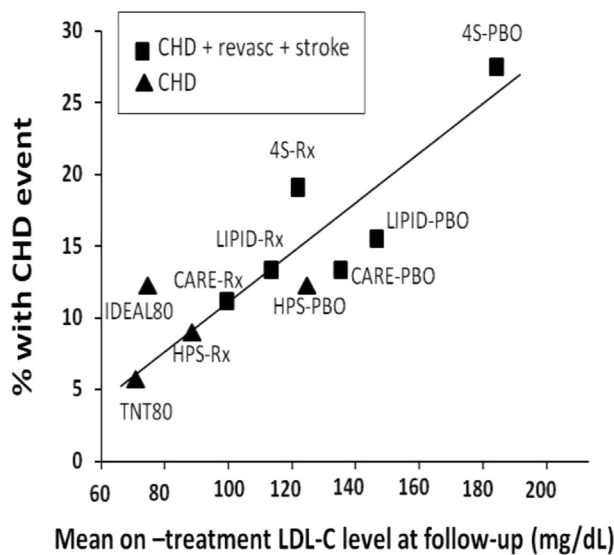
Figure 6 Relationship between on-treatment low-density lipoprotein cholesterol (LDL-C) concentration and coronary heart disease (CHD) events in studies of secondary prevention.[8,77–82]

ratio of 0.78) for major ASCVD events.[98] In addition, there was no evidence of an LDL-C threshold within the range studied. Larger LDL-C reductions, for example 2 to 3 mmol/L (77.4–116.1 mg/dL), could yield up to 40% to 50% relative risk reduction for ASCVD.

3. The intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event.

Available therapeutic options for lowering atherogenic cholesterol and reducing risk for an ASCVD event include lifestyle and drug therapies. Lifestyle therapy is considered to be first-line intervention and is nearly universally acknowledged to be appropriate and necessary for the management of dyslipidemia among individuals ranging from lowest to highest risk for ASCVD.[3,8,96,99] LDL-C (and non–HDL-C) reductions with lifestyle changes are most

Figure 7 Major CV event risk according to LDL-C and non–HDL-C levels achieved with statin therapy in a meta-analysis of statin trials.[97] CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol; Ref, referent.

often in the range of 5% to 15%,[4,100] an amount that, if maintained over a long period, may result in meaningful ASCVD risk reduction.[4,101] The relationship between the degree of change in atherogenic cholesterol concentration due to lifestyle changes and the difference in CHD risk aligns with the relationship for atherogenic cholesterol–lowering drug therapies.[96] However, in individuals at moderate to higher risk for ASCVD, a larger magnitude of atherogenic cholesterol lowering than can be achieved with lifestyle changes alone is generally warranted to substantially lower ASCVD risk. Decisions regarding the addition of atherogenic cholesterol–lowering drug therapy to lifestyle therapies for dyslipidemia management, as well as the intensity of the drug to be used, should include an investigation of the patient's absolute risk for ASCVD, including long-term risk (as described more fully within this document), tempered by clinical judgment and consideration of the interactions of cost, benefit, and safety of the drug therapies.

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 or lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies.

An early stage of atherosclerosis has been identified as fatty streaks in the coronary arteries of adolescents and young adults.[102–104] Long-term follow-up in prospective studies has demonstrated that elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle age.[51,105,106] Thus, lowering serum cholesterol levels earlier in life is likely beneficial for altering long-term or lifetime risk for developing ASCVD. Clinical trials of statins generally indicate that each 1% decrease in LDL-C concentration is associated with about a 1% decrease in risk for CHD.[53,107] However, results from epidemiologic and Mendelian randomization studies suggest a larger effect of lower LDL-C levels on CHD in groups with lower cholesterol levels throughout life.[56,101,108,109] This is consistent with the hypothesis that maintaining a lower serum cholesterol concentration for periods longer than the duration of typical clinical trials (averaging roughly 5 years) has the potential to yield a greater reduction in ASCVD risk than the approximate 1% to 1% relationship and supports the benefits of approaching risk-reduction therapy from a long-term or lifetime perspective.[110,111]

Many of the multivariate risk calculators that have been designed for clinical use in ASCVD risk assessment and to guide decisions for initiating drug therapy were created to predict intermediate-term (eg, 10 year) risk for an ASCVD event.[3,9] Short- and intermediate-term risk reduction has an important place in the management of dyslipidemia, particularly by reducing atherogenic cholesterol in patients with preexisting ASCVD to stabilize plaques and reduce the likelihood of acute coronary syndromes.[112] However,
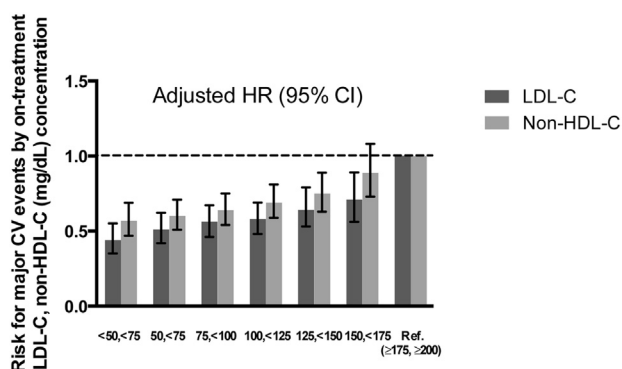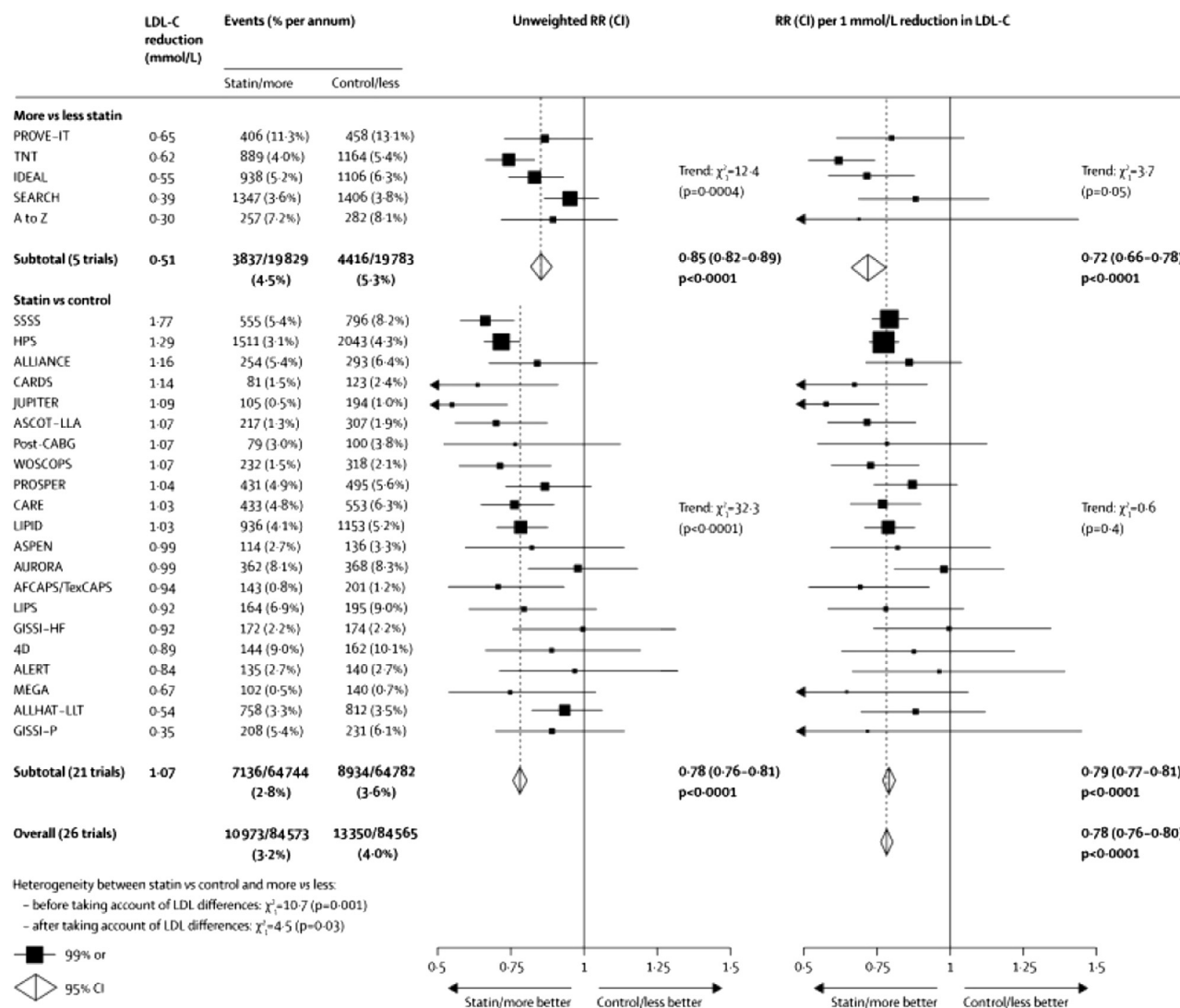
Figure 8   Effects of statin therapy on major vascular events.[98] In the left panel, unweighted rate ratios (RRs) for each trial of the comparison of the first event rates between randomly allocated treatment groups are plotted along with 99% confidence intervals (CIs). Trials are ordered according to the absolute reduction in low-density lipoprotein cholesterol (LDL-C) at 1 year within each type of trial comparison (more vs less statin and statin vs control). In the right panel, RRs are weighted per 1.0 mmol/L LDL-C difference at 1 year. Subtotals and totals with 95% CIs are shown by open diamonds. Taken from Cholesterol Treatment Trialists' (CTT) Collaboration.[98]

some individuals with a relatively low intermediate-term risk for an ASCVD event may have substantially elevated lifetime risk because of the presence of multiple or severe ASCVD risk factor disturbances. This is particularly the case for men <40 years and women <50 years of age with multiple or severe ASCVD risk factors,[113–115] and the NLA Expert Panel concluded that consideration of long-term or lifetime risk in such patients is useful for guiding treatment decisions.

5. For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk.

Statins block hepatic cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase and have been shown to reduce serum LDL-C

levels by 18% to 55%, non–HDL-C by 15% to 51%, and triglycerides by 7% to 30% (in hypertriglyceridemia, the reduction is typically by 20% to 50%, particularly with high-potency statins) and increase HDL-C by 5% to 15% (compiled from prescribing information). A large body of RCT evidence demonstrates that statins are safe and generally well tolerated by most patients and that they decrease risk for ASCVD events in both primary and secondary prevention in amounts proportional to their atherogenic cholesterol lowering (Fig. 8).[4,20,80,91,92,98,116] For these reasons, they are considered to be first-line drug treatment in both primary and secondary prevention of ASCVD. Although the predominant action of statins for reducing ASCVD risk is by lowering atherogenic lipoprotein concentrations, they may also have pleiotropic effects.[117–121]

Because of their favorable benefit to safety profile,[1] moderate- and high-intensity statins are reasonable for most patients. However, in hypercholesterolemic patients who are statin intolerant,[122] alternate atherogenic cholesterol–lowering drugs (eg, bile acid sequestrants, nicotinic acid, fibric acids, or cholesterol absorption inhibitor) or alternative statin dosing regimens may need to be considered.

6. Nonlipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus.

Atherogenic cholesterol lowering is the focus of dyslipidemia management, and therapies to lower cholesterol will reduce ASCVD risk even in the presence of other risk factors.[123–126] However, nonlipid ASCVD risk factors contribute to the acceleration of atherosclerosis and development of acute coronary syndromes.[127–131] When identified, these risk factors, particularly high blood pressure, cigarette smoking, and diabetes mellitus, require management to maximize ASCVD risk reduction.[2–4,8,11,132–134]

7. The measurement and monitoring of atherogenic cholesterol levels remain an important part of a comprehensive ASCVD prevention strategy.

Results from RCTs of a variety of atherogenic cholesterol–lowering therapies as well as results from observational studies have generally found that lower on-treatment atherogenic cholesterol levels are associated with lower ASCVD risk.[8,49,50,98,106] This suggests that treatment goals and periodic monitoring of atherogenic cholesterol are useful for allowing a clinician to match the aggressiveness of lipid-lowering therapy to a patient's absolute risk for an ASCVD event and for assessing the adequacy of a patient's response and adherence to therapy. Treatment goals and monitoring of atherogenic cholesterol are particularly valuable tools in patient–clinician communication.

Importance of lifestyle therapies

A key tenet of the NLA Expert Panel recommendations is the centrality of lifestyle therapies to ASCVD prevention. Lifestyle therapies for ASCVD risk reduction generally include interventions aimed at (1) altering the composition of the diet; (2) reducing total energy intake to lower body weight and adiposity for those who are overweight or obese; (3) increasing physical activity; (4) improving risk factors associated with the metabolic syndrome (adiposity, dyslipidemia, high blood pressure, and elevated plasma glucose); and (5) ceasing tobacco use. The NLA Expert Panel's specific recommendations regarding lifestyle therapy, and the rationale for those recommendations, will be explained fully in part 2.

The application of pharmacotherapy to dyslipidemia management has been enormously successful. Many large-scale RCTs, involving, in aggregate, hundreds of thousands of participants, have shown that drug therapies (particularly statins) that lower atherogenic cholesterol levels are effective for reducing ASCVD morbidity and mortality.[98,116] RCT evidence from studies examining lifestyle changes, and dietary interventions in particular, for reducing ASCVD risk is relatively less robust.[96,117] Furthermore, many of these trials were conducted several decades ago when dietary habits were much different from the typical American diet of today,[96,107] although results from some later RCTs also suggest benefits on ASCVD outcomes with dietary interventions.[135–137] Results from observational studies strongly suggest an influence of lifestyle habits on ASCVD outcomes that is likely to be mediated, at least in part, through effects on atherogenic cholesterol levels as well as other metabolic and hemodynamic disturbances such as obesity, hypertension, and insulin resistance.[138–140] Thus, although drug therapy may be needed in those with sufficient risk, the NLA Expert Panel's consensus view is that lifestyle therapies are an important element of risk-reduction efforts, whether or not drug therapy is also used. The beneficial impact of lower atherogenic cholesterol levels for reducing ASCVD risk is also supported by genetic studies of individuals with *PCSK9* mutations and with polymorphisms in the NPC1L1 protein, both of which result in reduced levels of LDL-C throughout life,[56–58] and by findings that genetic mutations resulting in modification of circulating levels of triglycerides and triglyceride-rich lipoprotein cholesterol (eg, variants associated with lipoprotein lipase, apo C3, and apo A5) are associated with altered ASCVD risk.[27,28,62,65–69]

Usefulness of treatment goals

Most RCTs of lipid-lowering drug therapies have tested drug treatment against a placebo control, or a more intensive with a less-intensive treatment regimen. The strategy of treating patients to a specific level of LDL-C or non–HDL-C has not been tested in any of the large trials assessing ASCVD morbidity and mortality. However, the lack of RCTs explicitly designed to test goals does not invalidate the considerable evidence supporting use of goals. Taken together, results from RCTs that have used various methods for lowering atherogenic cholesterol (pharmacotherapy, diet, and ileal bypass surgery) have indicated that lower on-treatment levels have been consistently associated with lower absolute risk for an ASCVD event.[8,37,98] These findings align with results from observational studies that suggest a log-linear relationship between the levels of atherogenic cholesterol and absolute ASCVD event risk.[49,50,106]

The Expert Panel's consensus view is that treatment goals, which have been used historically by health care

Table 1 Classifications of cholesterol and triglyceride levels in mg/dL

Non–HDL-C*	
<130	Desirable
130–159	Above desirable
160–189	Borderline high
190–219	High
≥220	Very high
LDL-C	
<100	Desirable
100–129	Above desirable
130–159	Borderline high
160–189	High
≥190	Very high
HDL-C	
<40 (men)	Low
<50 (women)	Low
Triglycerides	
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high[†]

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

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

[†]Severe hypertriglyceridemia is another term used for very high triglycerides in pharmaceutical product labeling.

providers for the past ∼25 years, continue to be useful as a systematic means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event.[141] Furthermore, the view is that using treatment goals, compared with prescribing moderate- to high-intensity statins without treatment targets, will not result in undertreatment as was suggested in the American College of Cardiology (ACC)/American Heart Association (AHA) 2013 dyslipidemia recommendations.[3] Moreover, treatment goals facilitate effective communication between patients and clinicians, providing an easily interpretable means through which the clinician can communicate progress toward meeting treatment objectives, thus supporting efforts to maximize long-term adherence to the treatment plan. Many patients have periods of nonadherence and nonpersistence with use of atherogenic cholesterol–lowering medications, including statins.[18,142] Follow-up cholesterol testing to monitor goal achievement may promote increased long-term adherence,[143] which has been shown to increase the clinical benefits of statin use in primary and secondary ASCVD prevention patients.[144] A very important point regarding the treatment goals recommended by the NLA Expert Panel is that the goal is less than the stated value. Simply achieving a non–HDL-C or LDL-C level equal to the threshold value of the treatment goal is not adequate or desirable, and, in some cases, the clinician may opt to treat to values well below the thresholds.

Screening and classification of initial lipoprotein lipid levels

In all adults (≥20 years of age), a fasting or nonfasting lipoprotein profile should be obtained at least every 5 years. At a minimum, this should include total cholesterol and HDL-C, which allows calculation of non-HDL-C (total-C – HDL-C). If fasting (generally 9–12 hours), the LDL-C level may be calculated, provided that the triglyceride concentration is <400 mg/dL.[29,145]

Classifications for lipoprotein lipid levels are shown in Table 1. Lipoprotein lipid levels should be considered in conjunction with other ASCVD risk determinants to assess treatment goals and strategies, as covered later in this report.

If atherogenic cholesterol levels (non–HDL-C and LDL-C) are in the desirable range, lipoprotein lipid measurement and ASCVD risk assessment should be repeated in 5 years, or sooner based on clinical judgment. Examples of changes that might prompt earlier rescreening include changes in ASCVD risk factors (including weight gain), a premature ASCVD event in a first-degree relative, evidence of ASCVD in the patient, or a new potential secondary cause of dyslipidemia. For those with atherogenic cholesterol in the desirable range, public health recommendations regarding lifestyle should be emphasized. Chart 1 summarizes the recommendations for screening of initial lipoprotein lipid levels.

Chart 1 Recommendations for screening of initial lipoprotein lipid levels

| Recommendations	Strength	Quality
A fasting or nonfasting lipoprotein profile including at least total-C and HDL-C should be obtained at least every 5 y.	E	Moderate
Lipoprotein lipid levels should be considered in conjunction with other ASCVD risk determinants to assess treatment goals and strategies.	E	Moderate
If non–HDL-C and LDL-C are in the desirable range, lipoprotein lipid measurement and ASCVD risk assessment should be repeated every 5 y, or sooner based on clinical judgment.	E	Moderate
For individuals with atherogenic cholesterol levels in the desirable range, public health recommendations regarding lifestyle should be emphasized.	E	Moderate
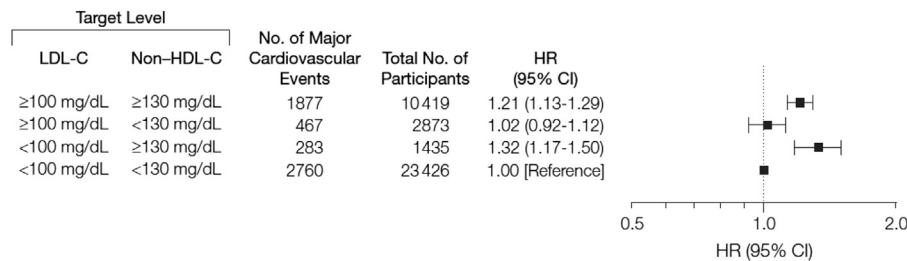
Figure 9 Risk of major cardiovascular events by low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non-HDL-C) categories.[153] Data markers indicate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of major cardiovascular events. Results are shown for 4 categories of statin-treated patients based on whether or not they reached the LDL-C target of 100 mg/dL and the non–HDL-C target of 130 mg/dL. HRs were adjusted for sex, age, smoking, diabetes, systolic blood pressure, and trial. Taken from Boekholdt SM et al.[153] with permission. Copyright © (2012) American Medical Association. All rights reserved.

Targets of intervention in dyslipidemia management

Non–HDL-C and LDL-C

When intervention beyond public health recommendations for long-term ASCVD risk reduction is used, levels of atherogenic cholesterol (non–HDL-C and LDL-C) should be the primary targets for therapies. LDL is the major atherogenic lipoprotein carrying cholesterol in a majority of patients, and LDL-C comprises ∼75% of the cholesterol in circulation carried by lipoprotein particles other than HDL, although this percentage may be lower in those with hypertriglyceridemia. Although LDL-C has traditionally been the primary target of therapy in previous lipid guidelines and in the practice of clinical lipidology, the NLA Expert Panel's consensus view is that non–HDL-C is a better primary target for modification than LDL-C. Non–HDL-C comprises the cholesterol carried by all potentially atherogenic particles, including LDL, IDL, VLDL and VLDL remnants, chylomicron particles and chylomicron remnants, and Lp (a). Epidemiologic studies have shown that non–HDL-C is a stronger predictor of ASCVD morbidity and mortality than LDL-C.[31,34,146–151] Pooled analyses of data from intervention studies have shown that non–HDL-C changes and levels during treatment are at least as strongly associated with risk for CHD as changes in LDL-C or on-treatment levels of LDL-C.[152,153] Moreover, when on-treatment values are discordant (ie, only 1 of the 2 is elevated), risk is more closely aligned with non–HDL-C than LDL-C (Fig. 9).[153,154]

Possible explanations for the superiority of non–HDL-C over LDL-C for predicting ASCVD event risk in those who are untreated and those receiving lipid-altering therapy include (1) as with LDL, some triglyceride-rich lipoprotein particles (remnants) enter the arterial wall and thus contribute to the initiation and progression of atherosclerosis; (2) non–HDL-C correlates more closely than LDL-C with apo B, thus may be a better indicator of the total burden of atherogenic particles[155–157]; (3) elevated levels of triglycerides and triglyceride-rich lipoprotein cholesterol

indicate hepatic production of particles with greater atherogenic potential, such as those having poor interactivity with hepatic receptors, resulting in longer residence time in the circulation[158]; and (4) elevated levels of triglyceride-rich lipoproteins, particularly in the postprandial state, may trigger an inflammatory response by monocytes, increasing their propensity to become macrophages.[159]

Although both non–HDL-C and LDL-C are termed atherogenic cholesterol, non–HDL-C is listed first to emphasize its primary importance. Both non–HDL-C and LDL-C are considered targets for lipid-altering therapy, and goals for therapy have been defined for both (Tables 2 and 3). Using non–HDL-C as a target for intervention also simplifies the management of patients with high triglycerides (200–499 mg/dL). An elevated triglyceride concentration confounds the relationship between LDL-C and ASCVD risk, even in cases when the triglyceride elevation is borderline, but this appears to be less of an issue with non–HDL-C.[29,160–162] Non–HDL-C incorporates the triglyceride level indirectly because the triglyceride concentration is highly correlated with the concentration of triglyceride-rich lipoprotein cholesterol.[27,36] Non–HDL-C testing is also preferable because it is calculated as the difference between 2 stable and easily measured parameters, total-C and HDL-C, and thus is less subject to artifact than LDL-C measurement or calculation.[29,144,148,163–167] Furthermore, non–HDL-C is more accurately measured in

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

Risk category	Treatment goal		
	Non–HDL-C	LDL-C	Apo B[*]
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very high	<100	<70	<80

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

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

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

Risk category	Criteria	Treatment goal Non–HDL-C, mg/dL LDL-C, mg/dL	Consider drug therapy 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.

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

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

the nonfasting state compared with LDL-C.[29,168] Goal levels of non–HDL-C may be attained by targeting either or both of the main components of non–HDL-C: LDL-C and VLDL-C. However, it should be emphasized that goal thresholds apply to both non–HDL-C and LDL-C, because discordance may occur, and effective management of atherogenic cholesterol would ideally result in achieving goal levels for both.

Desirable levels of atherogenic cholesterol for primary prevention (ie, those without clinical evidence of ASCVD or other very high-risk conditions) are <130 mg/dL for non–HDL-C and <100 mg/dL for LDL-C; for very high risk patients, the desirable levels are <100 mg/dL for non–HDL-C and <70 mg/dL for LDL-C (Tables 2 and 3). Support for these thresholds derives primarily from observational evidence showing low ASCVD incidence rates in groups with levels in these ranges.[4,8] In several studies, the risk for CHD was shown to decrease progressively to a total-C concentration of ~150 mg/dL, and populations with total-C below this level have low ASCVD morbidity
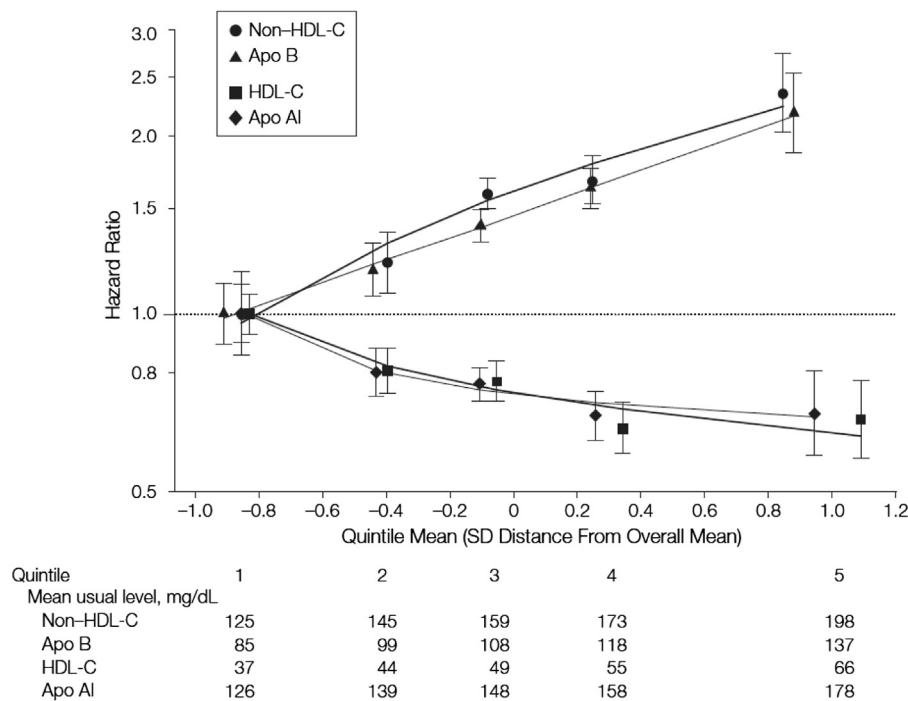
Figure 10 Hazard ratios for coronary heart disease across quintile of non–high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein (apo) B, HDL-C, and apo A1.[36] Analyses were based on 91,307 participants (involving 4499 cases) from 22 studies. Regression analyses were stratified, where appropriate, by sex and trial group and adjusted for age, systolic blood pressure, smoking status, history of diabetes mellitus, and body mass index; furthermore, analyses of non–HDL-C were adjusted for HDL-C and $\log_e$ triglyceride, analyses of apo B were adjusted for apo AI and $\log_e$ triglyceride, analyses of HDL-C were adjusted for non–HDL-C and $\log_e$ triglyceride, and analysis of apo AI were adjusted for apo B and $\log_e$ triglyceride. Studies with fewer than 10 cases were excluded from analysis. Sizes of data markers are proportional to the inverse of the variance of the hazard ratios. Referent groups are lowest fifths. Lines are fitted by first-degree fractional polynomial regression of log hazard ratios on mean SD score. Error bars indicate 95% confidence intervals. The y-axis is shown on a log scale. The x-axis is shown on a Z-transformed scale. Taken from Emerging Risk Factors Collaboration[36] with permission. Copyright © (2009) American Medical Association. All rights reserved. SD, standard deviation.

and mortality.[4,50,53] This corresponds to an LDL-C concentration of ~100 mg/dL. Examination of genetic variants that result in below-average levels of atherogenic cholesterol throughout life also support an LDL-C concentration of <100 mg/dL and a non–HDL-C level of <130 mg/dL for prevention of ASCVD.[56–58,68,169–172] Data from RCTs show that risk for ASCVD events is reduced with a variety of atherogenic cholesterol–lowering interventions, including cholesterol-lowering drugs and dietary modification, in a pattern that is generally consistent with expectations based on observational evidence.[8,37,83,116,173,174] An examination of the pravastatin-to-simvastatin conversion lipid optimization program cohort indicated that lipid-lowering therapy which reduced LDL-C to ≤100 mg/dL was associated with a significantly lower percentage of total and CHD-related deaths (40% vs 61%) compared with patients with LDL-C of >100 mg/dL.[175] The relationship between lower levels of atherogenic cholesterol with lower risk for ASCVD events has been shown to be present to LDL-C values of <55 mg/dL.[80–83,176–179]

The designation of non–HDL-C treatment targets as 30 mg/dL more than the LDL-C concentration is based on the assumption that "normal" VLDL-C concentration when triglycerides are <150 mg/dL is typically ≤30 mg/dL,

and when triglycerides are elevated, VLDL-C is typically >30 mg/dL.[4,180] In observational studies, each 1 mg/dL increment in triglyceride-rich lipoprotein cholesterol is associated with an increment in ASCVD event risk at least as large as that for each 1 mg/dL increase in LDL-C.[27,31,34,62,147] As further research is conducted to investigate the atherogenic properties of triglyceride-rich lipoproteins, including VLDL particles, the accepted values for typical VLDL-C and associated non–HDL-C targets may be modified.[181]

Apolipoprotein B

Apo B is considered an optional, secondary target for treatment. Epidemiologic studies have generally shown that both apo B and non–HDL-C are better predictors of ASCVD risk than LDL-C.[147,152] Because each potentially atherogenic lipoprotein particle contains a single molecule of apo B, the apo B concentration is a direct indicator of the number of circulating particles with atherogenic potential. Apo B and non–HDL-C share the advantage that neither requires fasting for accurate assessment. Non–HDL-C is favored over apo B by the NLA Expert Panel because it is universally available, requiring no additional expense
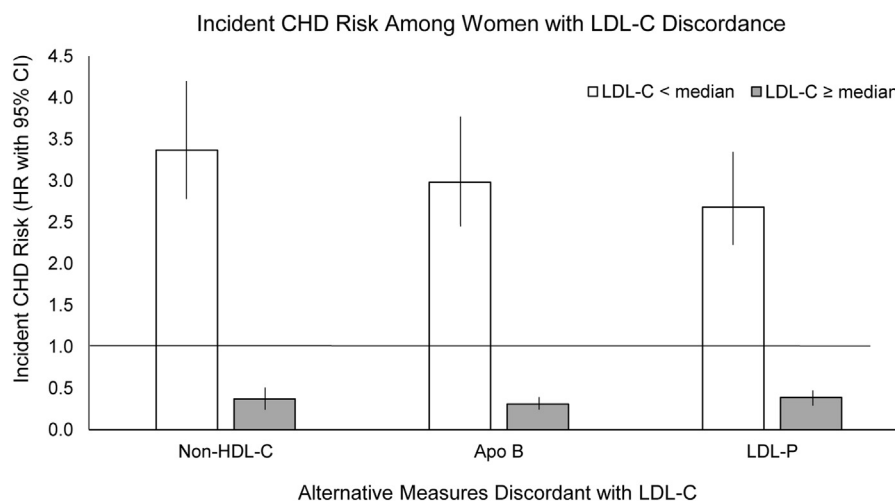
Incident CHD Risk Among Women with LDL-C Discordance

Figure 11 Hazard ratios (HR) ad 95% confidence intervals (CIs) for an incident coronary heart disease (CHD) event among women discordant for low-density lipoprotein cholesterol (LDL-C) and alternate measures of atherogenic lipoprotein burden.[70] Apo, apolipoprotein; LDL-P, low-density lipoprotein particle concentration; Non–HDL-C, non–high-density lipoprotein cholesterol.

compared with the standard lipid profile, and because apo B has not been consistently superior to non–HDL-C in predicting ASCVD event risk (Fig. 10).[36,153,173]

Cholesterol-lowering drug therapies, especially statins, alter the relationship between atherogenic cholesterol and apo B, often lowering the cholesterol concentration more than the apo B level. Apo B is a potential contributor to residual ASCVD risk because it may remain elevated in some individuals who have attained their treatment goals for non–HDL-C and LDL-C (discussed in the following section), particularly in patients with high triglycerides and low HDL-C levels.[70,161] A clinical trial assessing the ability of more aggressive lipid management to lower residual risk in patients on statin therapy, but with residual elevation in apo B (and/or LDL particle concentration), is needed. An examination of LDL-C, non–HDL-C, apo B, and LDL particle concentrations among 27,533 apparently healthy women in the Women's Health Study demonstrated reasonably high correlations between LDL-C and each of the alternate measures (non–HDL-C, apo B, and LDL particle concentration), but substantial discordance between measurements in some individuals (Fig. 11).[70] For those with concordant levels of LDL-C and non–HDL-C, apo B, or LDL particle concentration, the clinical utility of these measures for estimating coronary risk was similar. However, among the subgroups of subjects with discordance of LDL-C with another atherogenic lipoprotein-related measure such as non–HDL-C, apo B, or LDL particle concentration (11%-24% depending on the measure used), ASCVD risk was either overestimated or underestimated by 20% to 50% compared with LDL-C alone. Discordance has been defined variably in research conducted to date (eg, median cut points or guideline cut points).[70,153,182-185] Additional research will be needed to further elucidate the clinical importance of discordance between measures of atherogenic lipoprotein burden.

If apo B is used as an optional target for treatment, goals are <90 mg/dL for primary prevention and <80 mg/dL for those with very high risk, although measurement of apo B is generally not necessary until the patient has been treated to his or her goal levels for atherogenic cholesterol (Table 2).[186–188] The thresholds for these cut points represent the panel's consensus based on an evaluation of the available evidence and are consistent with those recommended previously by the American Diabetes Association/ACC Foundation.[186] Treatment with statins and other cholesterol-lowering drug therapies appears to alter the relationship between atherogenic cholesterol and apo B concentrations.[155,189–191] In an analysis of data from the Limiting Undertreatment of Lipids in ACS with Rosuvastatin (LUNAR) trial, Ballantyne et al[190] reported that during statin therapy, an apo B concentration of 90 mg/dL was associated with mean LDL-C and non–HDL-C concentrations of 85 and 105 mg/dL, respectively. The corresponding mean values associated with an apo B concentration of 80 mg/dL were 74 mg/dL for LDL-C and 92 mg/dL for non–HDL-C. As discussed previously, patients who remain above the apo B goals, despite having reached their atherogenic cholesterol goals, are discordant and may therefore have residual risk related to an elevated concentration of circulating particles with atherogenic potential.

Clinicians may consider measuring LDL particle concentration as an alternative to apo B.[161,183,188] Apo B and LDL particle concentration have been reported to perform similarly with regard to the prediction of increased ASCVD risk.[154,188] The NLA Expert Panel acknowledges that measurement of LDL particle concentration can be useful clinically, particularly once non–HDL-C and LDL-C goals have been attained, as another potential indicator of residual risk for ASCVD. The Centers for Disease Control–National Heart, Lung, and Blood Institute has standardization programs for LDL-C, non–HDL-C, and

Table 4   Criteria for clinical identification of the metabolic syndrome (any 3 or more of the listed components)[200]

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

HDL-C, high-density lipoprotein cholesterol.

*American Heart Association/National Heart, Lung and Blood Institute guidelines for metabolic syndrome suggest waist circumference thresholds of ≥37 inches (≥94 cm) in men and ≥32 inches (≥80 cm) in women as optional cut points for individuals or populations with increased insulin resistance, including those of Asian descent (alternate values have also been published for other groups).[8]

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

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

apo B measurements. A similar standardization program for LDL particle concentration has not yet been established. Most studies of LDL particle concentration published to date have used a proprietary nuclear magnetic resonance method,[183,188] but other proprietary methodologies for LDL particle concentration quantification are also available. These various methods appear to have variable agreement in terms of LDL particle size,[192–194] and their performance for predicting ASCVD risk has not been directly compared. Accordingly, the NLA Expert Panel did not recommend treatment goals for LDL particle concentration. Additional information about the clinical use of LDL particle concentration may be found in a report issued by another panel of NLA experts: Clinical Utility of Inflammatory Markers and Advanced Lipo–protein Testing: Advice from an Expert Panel of Lipid Specialists.[161]

Triglycerides

Prospective epidemiologic studies and meta-analyses have demonstrated a positive relationship between serum triglyceride levels and incidence of ASCVD,[195–197] although the mechanisms responsible for this association are not fully understood.[198] Possible pathophysiological links include (1) the atherogenicity of smaller species of triglyceride-rich remnant lipoprotein particles that may enter the subendothelial space; (2) elevated triglycerides may act a marker of increased concentrations of atherogenic particles (apo B–containing, apo C3–containing, small dense LDL particles); and (3) triglycerides are associated with other metabolic disturbances (insulin resistance, inflammation, endothelial dysfunction, hypercoagulation, and lower reverse cholesterol transport).[197–199] An elevated triglyceride concentration is also a component of the metabolic syndrome.[200] The NLA Expert Panel agreed that an elevated triglyceride level is not a target of therapy per

se, except when very high (≥500 mg/dL). When triglycerides are between 200 and 499 mg/dL, the targets of therapy are non–HDL-C and LDL-C.

Fasting triglyceride levels of ≥500 mg/dL (and especially ≥1000 mg/dL) are associated with increased risk of acute pancreatitis.[201] Although significant chylomicronemia generally does not occur until the fasting triglyceride level is substantially higher than 500 mg/dL (~750 mg/dL), there is no single threshold of triglyceride concentration above which pancreatitis may occur, and it can be exacerbated by other risk factors. A threshold of ≥500 mg/dL was selected to define very high triglycerides because the triglyceride level fluctuates markedly and such individuals are at risk for developing more severe hypertriglyceridemia.

A cohort study that examined the risk for acute pancreatitis according to the degree of hypertriglyceridemia (triglycerides <150, 150–499, or ≥500 mg/dL) in >65,000 subjects found a significant dose-response relationship between triglyceride concentration and incident acute pancreatitis during 15 years of follow-up. The risk increased 4% for each 100 mg/dL increase in triglyceride level (after adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related comorbidities, renal failure, and other biliary diseases).[202]

Thus, when the triglyceride concentration is very high (≥500 mg/dL, and especially if ≥1000 mg/dL), reducing the concentration to <500 mg/dL to prevent pancreatitis becomes the primary goal of therapy. There are limited clinical trial data to support the benefits of triglyceride-lowering therapy for reducing risk for pancreatitis.[203,204]

High-density lipoprotein cholesterol

Epidemiologic evidence suggests that HDL-C is inversely associated with ASCVD,[64,205,206] and the level of HDL-C is widely accepted as an important risk indicator

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

Drugs that elevate LDL-C	Drugs that elevate triglycerides
• Some progestins	• Oral estrogens
• Anabolic steroids	• Tamoxifen
• Danazol	• Raloxifene
• Isotretinoin	• Retinoids
• Immunosuppressive drugs (cyclosporine)	• Immunosuppressive drugs (cyclosporine, sirolimus)
• Amiodarone	• Interferon
• Thiazide diuretics	• Beta-blockers (especially non-beta 1 selective)
• Glucocorticoids	• Atypical antipsychotic drugs (fluperlapine, clozapine, olanzapine)
• Thiazolidinediones	• Protease inhibitors
• Fibric acids (in severe hypertriglyceridemia)	• Thiazide diuretics
• Long chain omega-3 fatty acids (in severe hypertriglyceridemia, if containing docosahexaenoic acid)	• Glucocorticoids
	• Rosiglitazone
	• Bile acid sequestrants
	• L-asparaginase
	• Cyclophosphamide

LDL-C, low-density lipoprotein cholesterol.

and used in risk factor counting and quantitative ASCVD risk assessment.[4,5,207] Low HDL-C is also a component of the metabolic syndrome. HDL particles have several properties that are expected to provide protection against ASCVD including reverse cholesterol transport, antioxidation, endothelial protection, antiplatelet activity, and anticoagulation,[208,209] but a direct mechanistic relationship between low HDL and ASCVD is not fully understood. It has been suggested that low HDL-C levels may simply be a reflection of the presence of other atherogenic factors, such as hypertriglyceridemia, particularly the degree of postprandial hypertriglyceridemia.[210,211] A Mendelian randomization approach to examine the potential causality of the relationship between HDL-C level and reduced risk for myocardial infarction in case-control and prospective cohort studies found that single nucleotide polymorphisms that increase plasma HDL-C concentration in isolation (ie, without altering triglycerides or LDL-C) were not associated with reduced risk of myocardial infarction.[212] To date, clinical trials of agents that markedly raise HDL-C, including niacin and cholesteryl ester transfer protein inhibitors, have failed to demonstrate that they reduce all cause mortality, CHD mortality, myocardial infarction, or stroke in statin-treated patients.[210,213–217]

The NLA Expert Panel did not rule out the possibility of a potential ASCVD risk-reduction benefit with raising HDL-C or promoting HDL function, but at this time, HDL-C is not recommended as a target of therapy per se. The HDL-C level is often raised as a consequence of efforts to reduce atherogenic cholesterol through lifestyle and drug therapies.

Metabolic syndrome

Metabolic syndrome is recognized as a multiplex risk factor for both ASCVD and type 2 diabetes mellitus (Table 4).[200] Available evidence from meta-analyses suggests that metabolic syndrome is independently associated with ASCVD risk, essentially doubling the risk.[218–221] The increased ASCVD risk with metabolic syndrome is generally considered to be above and beyond that associated with traditional ASCVD risk factors; the predictive

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

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

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

value of metabolic syndrome for type 2 diabetes mellitus risk, although substantial, is less than that shown for diabetes-specific risk equations.[200,222–224] Increased adiposity and insulin resistance appear to be central pathophysiological features of this cluster of interrelated metabolic and hemodynamic disturbances including elevations in blood pressure, triglycerides and glucose, as well as depressed HDL-C. The metabolic syndrome also likely reflects ASCVD risk secondary to indicators that are often not measured clinically including increased oxidation, inflammation, endothelial dysfunction, and thrombogenicity. Some of the NLA Expert Panel members were in favor of recommending that a diagnosis of metabolic syndrome be considered for reclassification of an individual into a higher risk category (ie, for risk refinement as described later in this document). However, because of the overlap between certain ASCVD risk factors and metabolic syndrome criteria (eg, HDL-C and triglycerides), the panel as a whole did not agree that the metabolic syndrome should be labeled a high risk condition at this time. The main value of identifying the presence of the metabolic syndrome is to recognize individuals with a high potential to benefit from lifestyle therapies, particularly weight loss if overweight or obese and increased physical activity. Successful lifestyle intervention will reduce adiposity and insulin resistance, improving multiple physiological disturbances that may contribute to risk, including the metabolic syndrome components as well as indicators of inflammation, oxidation, and thrombogenicity.[2,4,134,225–228]

Waist circumference thresholds are presented in the list of metabolic syndrome components in Table 4 because waist is generally considered to be a better indicator of abdominal obesity than body mass index (BMI).[229–231] However, members of the NLA Expert Panel recognized that waist is not always measured in clinical practice, whereas weight and height data for the calculation of BMI are usually available. Thus, although not the preferred indicator, BMI may be used as an alternative to waist circumference when the latter is not available.[232–234] Using National Health and Nutrition Examination Survey data, the cut points for BMI that produced the same population

Chart 2   Recommendations for targets of intervention in dyslipidemia management

Recommendations	Strength	Quality
When intervention beyond public health recommendations for long-term ASCVD risk reduction is used, levels of atherogenic cholesterol (non–HDL-C and LDL-C) should be the primary targets for therapies.	A	High
Goal levels of non–HDL-C may be attained by targeting either or both of the main components of non–HDL-C: LDL-C and VLDL-C.	B	Moderate
Desirable levels of atherogenic cholesterol for primary prevention are <130 mg/dL for non–HDL-C and <100 mg/dL for LDL-C. Goals for very high risk patients are <100 mg/dL for non–HDL-C and <70 mg/dL for LDL-C.	B for primary prevention; A for secondary prevention	Moderate for primary prevention; high for secondary prevention
Apo B is considered an optional, secondary target for treatment after the patient has been treated to goal levels for atherogenic cholesterol.	E	Moderate
Goals for apo B as an optional target for treatment are <90 mg/dL for primary prevention and <80 mg/dL for those with very high risk.	E	Low
Clinicians may consider measuring LDL particle concentration as an alternative to apo B	E	Moderate
Elevated triglyceride level is not a target of therapy per se, except when very high (≥500 mg/dL). • When triglycerides are between 200 and 499 mg/dL, the targets of therapy are non–HDL-C and LDL-C. • When triglycerides are very high (≥500 mg/dL, and especially if ≥1000 mg/dL), reduction to <500 mg/dL to prevent pancreatitis becomes the primary goal of therapy.	B for triglycerides 200–499 mg/dL; B for triglycerides ≥500 mg/dL	Moderate for triglycerides 200–499 mg/dL; low for triglycerides ≥500 mg/dL
HDL-C is not recommended as a target of therapy per se, but the level is often raised as a consequence of efforts to reduce atherogenic cholesterol through lifestyle and drug therapies.	N	Moderate
Metabolic syndrome is recognized as a multiplex risk factor for both ASCVD and type 2 diabetes mellitus, and its presence indicates high potential to benefit from lifestyle therapies.	B	Moderate
Some conditions or medications can produce adverse changes in lipid levels and should be considered when evaluating patients with dyslipidemia.	A	High

Table 7   Major risk factors for ASCVD*

1. Age
     Male ≥45 y
     Female ≥55 y
2. Family history of early CHD†
       <55 y of age in a male first-degree relative or
       <65 y of age in a female first-degree relative
3. Current cigarette smoking
4. High blood pressure (≥140/≥90 mm Hg, or on blood
    pressure medication)
5. Low HDL-C
     Male <40 mg/dL
     Female <50 mg/dL

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

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

†CHD is defined as myocardial infarction, coronary death, or a coronary revascularization procedure.

prevalence rates as the waist criteria were 25.0 kg/m² for women and 29.0 kg/m² in men.[232,233] Lower cut points of 23.0 and 27.0 kg/m² for women and men, respectively, may be considered for individuals or populations with increased insulin resistance, including those of East Asian, South Asian, or Native American descent.[8,200,235,236]

Secondary causes of dyslipidemia

Some conditions or medications can produce adverse changes in lipid levels and should be considered when evaluating patients with dyslipidemia.[3,237–244] Medications that may elevate levels of LDL-C and/or triglycerides are shown in Table 5. Conditions that may produce adverse changes in lipid levels are summarized in Table 6. Chart 2 summarizes the recommendations for targets of intervention in dyslipidemia management.

Table 8   Criteria for classification of ASCVD

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

ASCVD, atherosclerotic cardiovascular disease.

Table 9   High- or very high–risk patient groups

Quantitative risk scoring is not necessary for initial risk assessment in patients with the following conditions:*
- Diabetes mellitus, type 1 or 2
- Chronic kidney disease, stage ≥3B
- LDL-C ≥190 mg/dL: severe hypercholesterolemia phenotype, which includes FH
- ASCVD

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

*Patients in these categories are all at "high" or "very high" risk for an ASCVD event and should be treated accordingly.

ASCVD risk assessment and treatment goals based on risk category

In addition to lipoprotein lipid levels, ASCVD risk assessment includes evaluation of other major ASCVD risk factors (Table 7) and other conditions known to be associated with high or very high risk for an ASCVD event (Table 9). For high- and very high–risk patient groups (see the following for definitions), quantitative risk scoring (described in detail in the High risk section) will often underestimate ASCVD event risk so is generally not recommended unless a validated equation for that population subset is used.

ASCVD risk has been classified into 4 categories, as shown in Table 3. Risk category is used both for the purpose of defining treatment goals for atherogenic cholesterol (as well as apo B) and for defining the level of atherogenic cholesterol elevation at which pharmacotherapy to lower atherogenic cholesterol might be considered. However, it should be stressed that the NLA Expert Panel recommends consideration of the use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels, for patients with ASCVD or diabetes mellitus, based on RCT results that demonstrate a benefit in these patients at all levels of baseline lipids.[98] Lifestyle therapies should be emphasized and monitored in all patients with elevated levels of atherogenic cholesterol, whether or not pharmacotherapy for dyslipidemia management is used.

Risk assessment (Table 10) will often proceed according to the following steps:

- Step 1—identify high- and very high–risk conditions, if present.
    ○ Very high–risk conditions (Table 9)
        ■ Clinical ASCVD;
        ■ Diabetes mellitus (type 1 or 2) with ≥2 major ASCVD risk factors or evidence of end-organ damage (estimated glomerular filtration rate, <60 mL/min/1.73 m²).
    ○ High risk conditions (Table 9)
        ■ LDL-C of ≥190 mg/dL (severe hypercholesterolemia phenotype);
        ■ Type 1 or 2 diabetes mellitus with 0 to 1 major ASCVD risk factors;

Table 10   Sequential steps in ASCVD risk assessment

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

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

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

*End-organ damage indicated by increased albumin-to-creatinine ratio (≥30 mg/g), chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR], <60 mL/min/1.73 m^2), or retinopathy.

†For patients with CKD stage 3B (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.

‡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 CVD (myocardial infarction, CHD death or stroke) risk calculation. Clinicians may prefer to use other risk calculators, but should be aware that quantitative risk calculators vary in the clinical outcomes predicted (eg, CHD events, ASCVD events, cardiovascular mortality); the risk factors included in their calculation; and the timeframe for their prediction (eg, 5 years, 10 years, or long term or lifetime). Such calculators may omit certain risk indicators that can be very important in individual patients, provide only an approximate risk estimate, and require clinical judgment for interpretation.

Table 11   Additional risk indicators (other than major ASCVD risk factors) that might be considered for risk refinement[*]

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

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

*The presence of 1 or more of the risk indicators listed may be considered, in conjunction with major ASCVD risk factors, to reclassify an individual into a higher risk category. Except in the case of evidence of subclinical disease defining the presence of ASCVD, reclassification to a higher risk category is a matter of clinical judgment. Doing so will alter the threshold for consideration of pharmacotherapy and/or the treatment goals for atherogenic cholesterol. Many other ASCVD risk markers are available, but the National Lipid Association Expert Panel consensus view is that those listed have the greatest clinical utility. Some of the NLA Expert Panel members were in favor of recommending that a diagnosis of metabolic syndrome be considered a condition that could reclassify an individual into a higher risk category (ie, for risk refinement as described later in this document). However, because of the overlap between certain ASCVD risk factors and metabolic syndrome criteria (eg, HDL-C and triglycerides), the panel as a whole did not agree that the metabolic syndrome should be used for risk refinement at this time.

†Coronary artery calcium of ≥75th percentile for age, sex, and ethnicity. For additional information, see the Coronary Artery Calcium Score Reference Values web tool (http://www.mesa-nhlbi.org/CACReference.aspx).

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

- Chronic kidney disease (CKD) stage 3B or 4 (or estimated glomerular filtration rate, <45 but ≥15 mL/kg/1.73 m^2)
- Step 2—if none of the previously mentioned conditions is present, count major ASCVD risk factors and classify into the appropriate risk category.
  - 0 to 1 major ASCVD risk factor: low risk
  - 2 major ASCVD risk factors: moderate risk
  - ≥3 major ASCVD risk factors: high risk
- Step 3—Consider quantitative risk scoring and other factors for risk refinement, particularly in patients with moderate risk.
  - Quantitative risk scoring—thresholds are shown in the following for classification as high risk based on 3 commonly used risk calculators.
    - ATP III Framingham risk calculator: ≥10% 10-year risk for a hard CHD event (myocardial infarction or CHD death);
    - Pooled Cohort Equations (ACC/AHA): ≥15% 10-year risk for a hard ASCVD event (myocardial infarction, stroke, or death from CHD or stroke); and
    - Framingham long-term (30 year) risk calculator: ≥45% risk for CVD (myocardial infarction, CHD death, or stroke).
  - Other factors (Table 11)[161,245–256]—the presence of one or more of the following additional risk indicators may warrant moving the patient into a higher risk category based on clinical judgment.
    - Severe disturbance in a major ASCVD risk factor such as multipack per day smoking or strong family history of premature CHD
    - Indicators of subclinical disease, including coronary artery calcium (CAC; ≥300 Agatston units is considered high risk)
    - LDL-C ≥160 mg/dL and/or non–HDL-C ≥190 mg/dL
    - High-sensitivity C-reactive protein ≥2.0 mg/L
    - Lp (a) ≥50 mg/dL (protein) using an isoform-insensitive assay
    - Urine albumin-to-creatinine ratio ≥30 mg/g

Additional information about the 4 risk categories

Very high risk

Patients with clinical evidence of ASCVD, as defined in Table 8, and those with diabetes mellitus type 1[257,258] or 2 and ≥2 major ASCVD risk factors (Table 7), or evidence of end-organ damage, are considered to be at very high risk. These patients have the most aggressive goals for atherogenic cholesterol (non–HDL-C, <100 mg/dL; LDL-C, <70 mg/dL). For those at very high risk, pharmacotherapy is recommended when atherogenic cholesterol levels are above goal. In addition, pharmacotherapy with a moderate- or high-intensity statin is considered a therapeutic option in patients in this risk category even at lower pretreatment levels of atherogenic cholesterol. In particular,

use of a moderate- or high-intensity statin should be considered in patients with ASCVD or diabetes mellitus, irrespective of baseline atherogenic cholesterol levels.[98]

End-stage (stage 5) CKD is associated with very high risk for ASCVD events.[255,259,260] However, data from RCTs of lipid-altering therapies have not consistently shown benefits in this group.[261–264] Moreover, use of intensive lipid-lowering drug therapies in this group to achieve low levels of atherogenic cholesterol may not be practical. Therefore, goals for atherogenic cholesterol levels in stage 5 CKD have not been defined and are instead considered a matter of clinical judgment.

High risk

High-risk conditions include diabetes mellitus with 0 to 1 additional major ASCVD risk factors, CKD stage 3B or 4, or LDL-C of ≥190 mg/dL or the presence of ≥3 major ASCVD risk factors. As an option for those with 2 major ASCVD risk factors, the clinician may wish to perform quantitative risk scoring to estimate 10-year or long-term or lifetime risk for an ASCVD or CHD event. This step should generally be completed before investigation of other factors for risk refinement because the patient and health care system incurs no additional cost. This will facilitate identification of patients who may be classified as high risk in the absence of any of the high-risk conditions listed previously. The panel considers the threshold of high risk to be as follows for 3 of the most commonly used risk calculators:

- ATP III Framingham risk calculator (http://cvdrisk.nhlbi.nih.gov/calculator.asp): ≥10% 10-year risk for a hard CHD event (myocardial infarction or CHD death);
- Pooled Cohort Equations (ACC/AHA; http://tools.cardiosource.org/ASCVD-Risk-Estimator/): ≥15% 10-year risk for a hard ASCVD event (myocardial infarction, stroke, or death from CHD or stroke); and
- Framingham long-term (30 year) risk calculator (http://tools.cardiosource.org/ASCVD-Risk-Estimator/): ≥45% risk for CVD (myocardial infarction, CHD death, or stroke).

It should be noted that these thresholds are not intended to indicate "statin benefit groups" (ie, those in whom statin therapy has shown benefits regarding ASCVD event risk reduction) as used in the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[3]

In addition to the 3 described here, there are many other calculators available for use by the clinician to quantitatively estimate risk for ASCVD (see Goff et al[9] for a summary). 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 time frame 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. For clinicians who routinely measure high-sensitivity C-reactive protein, the Reynolds Risk Score, which incorporates high-sensitivity C-reactive protein, might be a good option (www.reynoldsriskscore.org).[265]

Results from primary prevention RCTs show that the relative risk for ASCVD events is reduced with statin therapy compared with control groups in whom incidence rates for ASCVD are relatively low (approximately 5.0%–7.5% 10-year risk projected from rates observed over shorter observation periods).[74,76,266]

The threshold of ≥10% 10-year risk for a hard CHD event using the ATP III Framingham Risk calculator was selected because it is roughly equivalent to 15% ASCVD risk, assuming the risk for stroke represents approximately one third of ASCVD events.[3,4,9,267] The threshold of ≥15% 10-year risk for a hard ASCVD event using the ACC/AHA Pooled Cohort Equations is higher than that recommended by the ACC/AHA for identification of a primary prevention statin benefit group.[3,9] The NLA Expert Panel was concerned that the Pooled Cohort Equations may overestimate risk in the current US population, resulting in overtreatment of some groups, particularly the elderly.[268,269]

The Pooled Cohort Equations have been found to perform well in some cohorts,[270] but appear to overestimate risk in others.[9,271–273] They have not undergone a prospective 10-year validation to date, and one possible reason for overestimation of risk is that ASCVD event risk has been declining in the US population.[19] The NLA Expert Panel view was that evidence from RCTs of statin therapy justified lowering the thresholds for consideration of drug therapy that were recommended in the NCEP ATP III guidelines. High risk was defined by the NLA Expert Panel as the threshold that defined "moderately high risk" in the 2004 ATP III update.[20] Some panel members expressed concern that the threshold for consideration of drug therapy in the ACC/AHA recommendations might be too low, particularly for older patients in whom age is the main factor responsible for crossing the 7.5% threshold. This will likely result in a smaller group that would potentially qualify for drug therapy, particularly among older individuals with a low burden of ASCVD risk factors other than age. The panel viewed measurement of CAC as a particularly useful tool for assisting with decisions about whether to use lipid-altering drug therapy in patients who fall into the range of 7.5% to 14.9% 10-year risk based on the Pooled Cohort Equations, or between 5.0% and 9.9% based on Framingham risk scoring.

Assessment of lifetime risk is now accepted as an important aspect of risk assessment, particularly among younger individuals (<50 years of age).[3,113] Long-term ASCVD event risk increases with both the number and severity of major risk factors.[113,274] Counting of major risk factors is most useful for long-term risk estimation, and has greater utility for this purpose than for assessing intermediate-term risk.[274] The NLA Expert Panel

recommendation for the high-risk threshold of ≥45% using the Framingham long-term (30 year) risk calculator was selected based on performance of the risk calculator in participants in the Framingham Heart Study[113,114] and the Cardiovascular Lifetime Risk Pooling Project.[274] Among Framingham Heart Study participants who were free of CVD at 50 years of age, lifetime risks to 95 years of age were estimated to be 51.7% for men and 39.2% for women.[113] The NLA approach considers high long-term risk as a finding that might alter the decision to use pharmacologic therapy, based on the causal-exposure paradigm, with the view that the injurious action of exposure to elevated levels of atherogenic cholesterol occurs over an extended period and preventive efforts earlier in the process are likely to be effective for arresting the initiation and progression of atherosclerotic disease.[111]

Scoring calculators based on population statistics provide only an approximate risk estimate for individual patients and require clinical judgment for interpretation. This is particularly true when applied to groups that may differ in average risk level compared with the population from which the equations were developed,[273] and in some cases even when applied to the same population with characteristics that may have changed over time.[272] There is no prospective evidence from RCTs that quantitative risk scoring is optimal for evaluating the need for lipid-altering therapies because trials of lipid-altering therapies have generally enrolled patients according to individual risk factors, particularly atherogenic cholesterol level, and not according to quantitative risk scores.[271,272] Furthermore, the uptake and utilization of quantitative risk scoring in clinical practice is rather low, resulting in underuse of lipid-altering therapies in those with multiple risk factors and diminished control of atherogenic cholesterol.[275] Risk equations should generally not be used in patients who have already been treated for dyslipidemia[276] and should not be used in individuals with FH because they underestimate risk. In some patients, the ASCVD risk estimate will be in the moderate- or high-risk category based primarily on nonlipid risk factors such as smoking or hypertension. In such cases, attention to these risk determinants may be most important.

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

Moderate risk

Individuals with 2 major ASCVD risk factors, in the absence of conditions that place them into the high- or very high–risk categories, are considered to be at moderate risk

(approximately 5% to <15% 10-year risk for an ASCVD event). Quantitative risk scoring and, in selected cases, evaluation of one or more additional risk indicators (Table 11) may be performed to identify those who should be reclassified as high risk (see the previous section).

Categorical risk factor counting and quantitative risk assessment provide similar results in most cases. Quantitative risk scoring may be helpful to refine decisions about risk stratification by accounting for variability in risk factor level or intensity and interactions between age and ASCVD risk factors.[4] It also provides an estimate of absolute risk, which may be useful as an educational tool. The NLA Expert Panel recommends consideration of those indicators of risk that do not result in additional cost to the patient, including quantitative risk scoring, first. If uncertainty persists after doing so, the expense of obtaining assessments of one or more additional risk indicators (Table 11) might be considered.

In some patients, 10-year risk for an ASCVD event may be lower than the high-risk threshold, but lifetime risk may be substantially elevated. This is especially true in women and younger adults (<50 years of age). In such individuals, calculation of long-term or lifetime risk may be particularly useful as an adjunct to the 10-year ASCVD or CHD event risk.[113,114] However, most risk equations do not incorporate additional risk indicators, which may be important to consider in specific patients.

The greatest potential utility exists for assessment of additional risk indicators among patients with 2 major ASCVD risk factors to identify those for whom the threshold for consideration of pharmacotherapy could be lowered. Indicators that might be considered for risk refinement are shown in Table 11 and include a severe disturbance in a single major ASCVD risk factor (eg, strong family history of CHD or multipack per day smoking)[245,246,254]; LDL-C ≥160 mg/dL and/or non–HDL-C ≥190 mg/dL; Lp (a) ≥50 mg/dL[161,252]; high-sensitivity C-reactive protein ≥2 mg/L[161]; an indication of subclinical disease, including elevated CAC ≥300 Agatston units[250,251]; or urine albumin-to-creatinine ratio ≥30 mg/g as a marker of increased CKD and ASCVD risk.[255]

The cut points for increased risk for Lp (a) and C-reactive protein were selected based on the recommendations of the 2011 NLA Expert Panel evaluation of biomarker assessments.[161] The ASCVD risk predictive power of Lp (a) appears to be independent and additive to other ASCVD risk factors including LDL-C and non–HDL-C concentrations.[252] An Lp (a) concentration of ≥50 mg/L represents approximately the 80th percentile of the general population.[161,252] C-reactive protein, which generally reflects the level of inflammation, is also a marker of risk for ASCVD events.[161,247–249] The selected cut point of ≥2.0 mg/L corresponds to the midpoint of the middle population tertile (1.0–3.0 mg/L) of high-sensitivity C-reactive protein approximated from >15 populations.[247]

CAC has incremental prognostic value for evaluating risk for an ASCVD event.[250,251,277–284] The threshold for

CAC of ≥300 Agatston units was chosen as an indicator of high risk based on population data, which demonstrated that a CAC score of >300, compared with a CAC of 0, was predictive of risk for myocardial infarction or CHD death among asymptomatic individuals with coronary risk factors (ie, moderate risk).[9,250,251,285] However, the CAC score should be interpreted in the context of the age, sex, and race or ethnicity of the patient.[281,286–288] Therefore, a value ≥75th percentile for the patient's age, sex, and race or ethnicity may also be used as an indicator of high-risk status (calculator from the MESA Coordinating Center available at http://www.mesa-nhlbi.org/CACReference.aspx).[281] In some patients, the 75th percentile may yield a CAC threshold well below 300 Agatston units. For example, in a 60-year-old black (African American) male, the 75th percentile for CAC is 40 Agatston units.[289]

An investigation of the impact of novel risk markers used in risk refinement, including CAC and high-sensitivity C-reactive protein, on ASCVD risk assessment using different cardiovascular risk equations demonstrated that incorporation of MESA-defined low-risk (0 Agatston units), high-risk (100 Agatston units), and very high–risk (400 Agatston units) CAC thresholds into validated risk equations resulted in greater changes in absolute cardiovascular risk than incorporation of high-sensitivity C-reactive protein values (thresholds of 1.0, 3.0, and 7.0 mg/L for low-, high-, and very high–risk, respectively).[290] It should be recognized that thresholds or cut points in these risk factors represent relative risk on a continuum and should not be misinterpreted as either the absence or presence of such risk at values above or below that threshold. As additional data become available regarding prediction, discrimination, and accuracy, it should be possible to more clearly define optimal strategies for application of these tests for additional ASCVD risk indicators in clinical practice.[268]

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

Low risk

Individuals with 0 or 1 major ASCVD risk factors are generally at low risk for an ASCVD event (<5% 10-year ASCVD event risk). Quantitative risk scoring is not typically necessary for such patients. Lifestyle therapies are the primary modalities for management of atherogenic cholesterol levels in such patients, although consideration may be given to pharmacotherapy in those with non–HDL-C of 190 to 219 mg/dL (LDL-C of 160 to 189 mg/dL).

If information about additional risk indicators or subclinical disease is known for patients with 0 to 1 risk factors, this should be considered when assigning the risk category and in making decisions about the use of pharmacotherapy.

Chart 3   Recommendations for ASCVD risk assessment and treatment goals based on risk category

| Recommendations	Strength	Quality
ASCVD risk assessment includes lipoprotein lipid levels, evaluation of other major risk factors, clinical evidence of ASCVD, and other conditions known to be associated with high or very high risk for an ASCVD event (LDL-C, ≥190 mg/dL; type 1 or 2 diabetes mellitus; and CKD stage 3B or higher).	A	High
Quantitative risk scoring is generally not recommended for high-risk and very high–risk groups, unless a validated equation for that population subset is used.	E	Low
ASCVD risk category is used for defining treatment goals for atherogenic cholesterol (and apo B) and for defining the level of atherogenic cholesterol elevation for which pharmacotherapy to lower atherogenic cholesterol might be considered.	A	Moderate
Lifestyle therapies should be emphasized and monitored in all patients with elevated levels of atherogenic cholesterol, whether or not pharmacotherapy for dyslipidemia management is used.	A	Moderate
Patients with clinical evidence of ASCVD and patients with diabetes and ≥2 major ASCVD risk factors or evidence of end-organ damage are at very high risk; drug therapy is recommended for patients with atherogenic cholesterol levels above goal. • Non–HDL-C goal is <100 mg/dL • LDL-C goal is <70 mg/dL	A	High
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.	A	High
Goals for atherogenic cholesterol levels for patients with stage 5 CKD are considered a matter of clinical judgment.	A	High
Patients with ≥3 major ASCVD risk factors or a high-risk condition (diabetes mellitus with 0–1 additional major ASCVD risk factors, CKD stage 3B or 4, or LDL-C ≥190 mg/dL) are at high risk; consideration of drug therapy is recommended for those with atherogenic cholesterol levels above goal after initiation of lifestyle therapy. • Non–HDL-C goal is <130 mg/dL • LDL-C goal is <100 mg/dL	A	High
In some high-risk patients, drug therapy may be started concurrently with lifestyle therapy (eg, those who are might be unlikely to attain atherogenic cholesterol goal levels without drug therapy or with diabetes mellitus and 0–1 other major ASCVD risk factors).	B	Moderate
Patients with 2 major ASCVD risk factors, in the absence of conditions that place them into the high- or very high–risk categories, are at moderate risk; consideration should be given to drug therapy in those with values at least 30 mg/dL above goal levels after initiation of lifestyle therapy. • Non–HDL-C goal is <130 mg/dL • LDL-C goal is <100 mg/dL	A	High
Patients with 0 or 1 major ASCVD risk factors are generally at low risk for an ASCVD event, and quantitative risk scoring is generally not necessary. Lifestyle therapies are the primary modality for management, but consideration may be given to pharmacotherapy when non–HDL-C is 190 to 219 mg/dL (LDL-C, 160–189 mg/dL). • Non–HDL-C goal is <130 mg/dL • LDL-C goal is <100 mg/dL	A	Low
Quantitative risk scoring to estimate 10-y or long-term or lifetime risk for an ASCVD or CHD event is an option for patients with 2 major ASCVD risk factors, in the absence of any high-risk conditions, to facilitate identification of high risk. Thresholds of high risk include the following: • ≥10% 10-y risk for a hard CHD event (ATP III Framingham) • ≥15% 10-y risk for a hard ASCVD event (Pooled Cohort Equations) • ≥45% risk for CVD (Framingham long-term, 30-y risk)	E	Low
When there is uncertainty about assigning risk category and the value of initiating pharmacotherapy, consideration of those indicators of risk that do not result in additional cost to the patient, including quantitative risk scoring, should generally be considered first.	E	Low
Additional risk indicators including a severe disturbance in a major ASCVD risk factor, indicators of subclinical disease (CAC, ≥300 Agatston units), LDL-C ≥160 mg/dL and/or non–HDL-C ≥190 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, Lp (a) ≥50 mg/dL, and urine albumin-to-creatinine ratio ≥30 mg/g should be considered when there is uncertainty about assigning risk category and the value of initiating pharmacotherapy.	E	Moderate
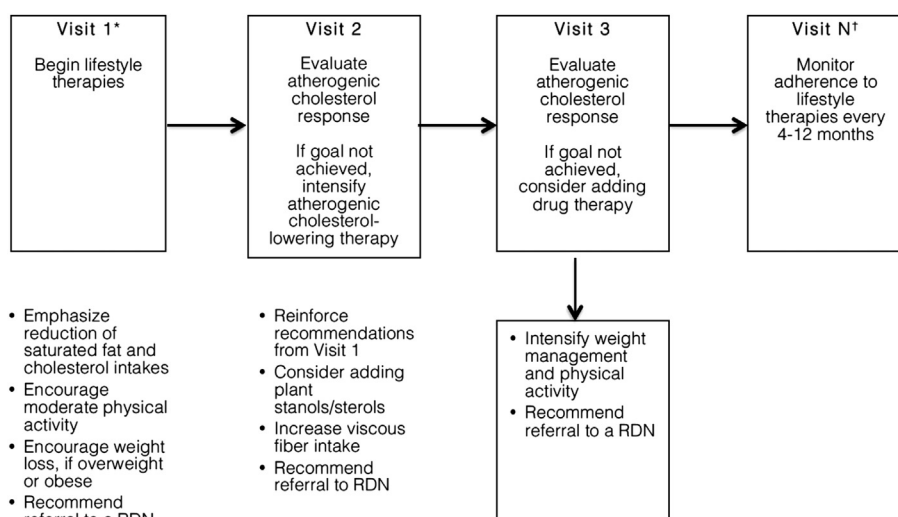
Figure 12 Model of steps in lifestyle therapies. *For people at high or very high risk for atherosclerotic cardiovascular disease in whom drug therapy is indicated, it may be started concomitantly with lifestyle therapies. For other patients, a trial of lifestyle therapies should be undertaken before the initiation of drug therapy. †In most cases, goal levels should be achieved in approximately 6 months. RDN, registered dietitian nutritionist.

In some individuals, a severe disturbance in a single major ASCVD risk factor, a known disturbance in an additional risk indicator, or evidence of subclinical disease (Table 11) might justify classifying the patient into the moderate- or the high-risk category, prompting consideration of pharmacotherapy at lower levels of atherogenic cholesterol. For CAC, a value in the range of 100 to 299 Agatston units, but below the age- and sex-specific 75th percentile, would justify assignment to the moderate-risk category in an otherwise low-risk patient.[283,285,289,291,292] Values of CAC of ≥300 Agatston units or ≥75th percentile would be considered high risk as described in the previous section.[250,251,289] Chart 3 summarizes the recommendations for ASCVD risk assessment and treatment goals based on risk category.

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

Lifestyle therapies

Figure 12 shows a model of the steps in application of lifestyle therapies. For patients at low or moderate risk, lifestyle therapies should be given an adequate trial (at least

3 months) before the use of drug therapy is considered. In patients at very high risk, drug therapy may be started concurrently with lifestyle therapies. This may also be the case for selected patients in the high risk category if the clinician feels it is unlikely that lifestyle therapies alone will be sufficient to reach goal, or if the patient has a high-risk condition such as diabetes mellitus or CAC of ≥300 Agatston units.

Visit 1

Typical lifestyle therapies for hypercholesterolemia include a diet low in saturated fat (<7% of energy), moderate or higher intensity physical activity (≥150 min/wk), and weight loss (5%–10% of body weight) for those who are overweight or obese. Where available, referral to a registered dietitian nutritionist (RDN) is recommended to facilitate dietary modification and to an exercise specialist for guided instruction on a suitable exercise program.[293,294] Lifestyle therapies will be described in greater detail in part 2 of these NLA Expert Panel recommendations.

Visit 2

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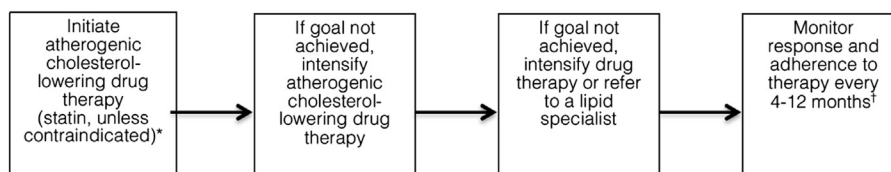

Figure 13 Progression of atherogenic cholesterol–lowering drug therapy.*A moderate- or high-intensity statin should be first-line drug therapy for treatment of elevated levels of atherogenic cholesterol, unless contraindicated. In a patient with very high triglycerides (≥500 mg/dL), a triglyceride-lowering drug may be considered for the first-line use to prevent pancreatitis. Other atherosclerotic cardiovascular disease risk factors should be managed appropriately in parallel. †In most cases, goal levels should be achieved in approximately 6 months.

other lifestyle recommendations should be reinforced, and referrals to an RDN and exercise specialist are recommended.

Visit 3

If goal levels of atherogenic cholesterol have been attained, responses to therapy should be monitored at intervals of 6 to 12 months. Note that moderate- or high-intensity statin therapy should be considered for very high–risk patients irrespective of atherogenic cholesterol levels. If goal levels have not been attained and the patient's levels remain above the threshold for consideration of drug therapy, drug treatment might be initiated.

Cholesterol-lowering drug therapies

Figure 13 shows a model for progression of atherogenic cholesterol–lowering drug therapy. When used, drug therapy should generally be initiated with moderate- to high-intensity statin therapy to take advantage of demonstrated ASCVD risk–reduction benefits.[80,91,98,116]

Patient-centered approach

Before initiation of lipid-lowering drug therapy for ASCVD risk reduction, the clinician should have a discussion with the patient about treatment objectives, as well as the potential for adverse effects, possible interactions with other drugs or dietary supplements, lifestyle and medication adherence, and patient preferences. Drug therapy for elevated levels of atherogenic cholesterol is generally maintained for an extended period. A large percentage of patients (more than 50% in some studies) prescribed a lipid-lowering drug discontinue refilling the prescription within 1 year.[295] Therefore, a discussion with the patient of the importance of continued adherence to achieve ASCVD event risk reduction is important. The clinician should convey that alternative agents and regimens are available in the event that side effects occur with a given medication or dosage level.

Thresholds for consideration of drug therapy

Because of the availability of inexpensive, generic statin medications with favorable safety and tolerability profiles, and demonstrated efficacy for reducing ASCVD event risk, even in relatively low-risk patients, the NLA Expert Panel consensus view is that risk thresholds for initiating drug treatment should be lowered as compared with the NCEP ATP III[4,20] but raised as compared with ACC/AHA 2013 recommendations.[3,296] Although these medications may be relatively inexpensive and well tolerated, overuse would result in unnecessary side effects (eg, myalgia leading to medication discontinuance, increased risk of raised blood sugar levels, and the development of type 2 diabetes) and ancillary costs including burden on the health care system (eg, physician visits, laboratory testing).[297,298] Based on the ACC/AHA 2013 guidelines, most men >60 years of age and most women >70 years of age would be eligible for statin therapy.[3]

Recommendations on such matters always involve a tradeoff between sensitivity (capturing the greatest fraction

Table 12   Intensity of statin therapy[*]

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

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

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

of the potential risk reduction in the population) and specificity (minimizing the number treated who would not have experienced an ASCVD event). The thresholds selected represent the consensus views of the NLA Expert Panel. Some clinicians may prefer to prescribe drug therapy (mainly statin treatment) to patients with lower levels of risk or atherogenic cholesterol. Such an approach may be considered based on clinical judgment and patient preferences in light of data from primary prevention RCTs showing ASCVD event risk reduction with statin therapy compared with control groups with projected 10-year ASCVD event rates as low as approximately 5% to 7.5%.[3,74,76,266]

Initiation of drug therapy

Unless contraindicated, first-line drug therapy for treatment of elevated atherogenic cholesterol levels is a moderate- or high-intensity statin (see Table 12 for statin intensity categories). A moderate-intensity statin will generally lower LDL-C by 30% to <50% and a high-intensity statin by ≥50%, although individual patient responses should be expected to vary considerably.[20,98,299] Some clinicians prefer to start with a high-intensity statin and reduce the dosage if the patient experiences intolerance. Others prefer to start with a moderate-intensity statin and titrate upward if additional lowering of atherogenic cholesterol is desired. Because patients commonly discontinue therapy when they experience side effects,[18,142,295] it is important for the clinician to apply the strategy that he or she feels will produce the greatest likelihood of long-term adherence in a given patient. However, if drug therapy is used, the panel consensus view was that at least a 30% reduction in atherogenic cholesterol should be targeted.[8]

Some patients have contraindications for, or intolerance to, statin therapy. For such patients, nonstatin drug therapy may be considered. Nonstatin drug classes for lipid management include cholesterol absorption inhibitor, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid.[300] Cholesterol absorption inhibitor, bile acid sequestrants, fibric acids, and nicotinic

Table 13 Drugs affecting lipoprotein metabolism

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

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

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

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

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

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

‖Gemfibrozil, fenofibrate, and fenofibric acid.

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

acid have been shown to reduce CHD or ASCVD event rates in placebo-controlled RCTs.[4,83–85,301–303] A summary of the lipid effects of the main classes of drugs available in the United States for treatment of dyslipidemia is shown in Table 13. Two additional classes of medications are also available with more limited indications for the treatment of patients with homozygous FH: mipomersen—an antisense oligonucleotide that targets the messenger RNA for apo B[304] and lomitapide—a microsomal triglyceride transfer protein inhibitor.[305]

Follow-up visits

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

In some patients taking high-intensity statin therapy, atherogenic cholesterol levels may drop to low levels (eg, LDL-C, <40 mg/dL). At present, no evidence suggests harm with such low circulating cholesterol levels, and therapy may be continued in such patients, particularly those at very high ASCVD event risk, in the absence of signs or symptoms of intolerance.[98,176,306,307] The limited amount of data available at these low levels is acknowledged, and the NLA Expert Panel awaits analyses from ongoing (eg, with the PCSK9 inhibitors) or recently completed trials (https://clinicaltrials.gov/ct2/show/NCT01624142)[83] to provide a more robust data set for cholesterol levels in these very low ranges.

Monitoring of atherogenic cholesterol levels is also important from the perspective of the evaluation of health care systems.[141] Information on attainment and maintenance of goal levels of atherogenic cholesterol allows mechanisms to be implemented for providing feedback to providers regarding quality of health care delivery.[295] Early and frequent follow-up by physicians (especially lipid testing) has been shown to be associated with improved adherence to lipid-lowering therapy.[308] A randomized prospective study is needed to determine whether this relationship is causal.

Management of patients with hypertriglyceridemia

For patients with very high triglycerides (≥500 mg/dL), the primary objective of therapy is to lower the triglyceride level to <500 mg/dL to reduce the risk of pancreatitis.[197,201] For patients with hypertriglyceridemia who have high triglycerides (200–499 mg/dL), the primary objective of therapy is to lower levels of atherogenic cholesterol (non–HDL-C and LDL-C) to reduce risk for an ASCVD event.

Lifestyle interventions are a key to efforts to reduce triglycerides, including weight loss if overweight or obese (initially targeting loss of 5%-10% of body weight), physical activity (≥150 min/wk of moderate or higher intensity activity), and restriction of alcohol and sugar or refined carbohydrate intakes.[197,226,309]

For those with very high triglycerides (≥500 mg/dL), chylomicronemia will often be present (essentially all patients with fasting triglycerides of ≥750 mg/dL will demonstrate chylomicronemia).[310] For such patients, a low-fat diet (<15% of energy) may be helpful to reduce entry of new chylomicron particles into the circulation.[311] For patients with triglycerides of <500 mg/dL, partial replacement of dietary carbohydrate (especially sugars and other refined carbohydrates) with a combination of unsaturated
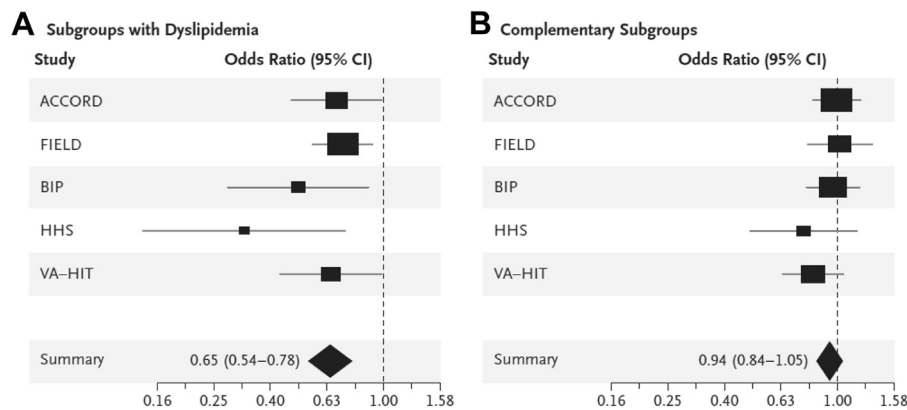
Figure 14   Reduction in the rate of coronary heart disease (CHD) events in subgroups of subjects with dyslipidemia from randomized controlled trials (RCTs) of fibrates.[327] Data from a meta-analysis of randomized trials of fibrate drugs are shown; an odds ratio of less than unity indicates a beneficial effect. (A) Data from subgroups of patients with dyslipidemia (ie, high levels of triglycerides and low levels of high-density lipoprotein cholesterol [HDL-C]) and (B) data from complementary subgroups without this type of dyslipidemia. The subgroup with dyslipidemia defined according to criteria prespecified in the ACCORD Lipid trial (a triglyceride level of ≥204 mg/dL and an HDL-C level of ≤34 mg/dL) and the subgroup with levels closest to these lipid criteria in each of the other trials were used. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, the cutoff triglyceride level was ≥204 mg/dL and the HDL-C level was <40 mg/dL in men or <50 mg/dL in women. In the Bezafibrate Infarction Prevention (BIP) study, the triglyceride level was ≥200 mg/dL and the HDL-C level was <35 mg/dL. In the Helsinki Heart Study (HHS), the triglyceride level was >204 mg/dL and the HDL-C was <42 mg/dL. In the Veterans Affairs HDL Intervention Trial (VA-HIT), the triglyceride level was >180 mg/dL and the HDL-C level was <40 mg/dL. The outcome defined for the subgroup analysis in each trial was used. The subgroups with dyslipidemia in all 5 studies included a total of 2428 study participants and 302 events among the patients who received fibrate therapy and 2298 study participants and 408 events among those who received placebo. A random-effects meta-analysis was used. The area of the rectangles is proportional to the precision of the study-specific estimated effect. The horizontal lines indicate the 95% confidence intervals (CIs) for study-specific odds ratios. The diamonds represent the summary odds ratios, with the width indicating the 95% CI. From Sacks FM et al.[327] Copyright © (2010) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

fats and proteins may help to reduce the triglyceride and non–HDL-C concentrations.[197,226,309,312]

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

For patients with high triglycerides (200–499 mg/dL), a statin will generally be first-line drug therapy. Statins are the most effective agents for reducing levels of atherogenic cholesterol and apo B, and evidence from hypertriglyceridemic subgroups in RCTs shows that statins lower ASCVD event risk in patients with elevated triglycerides in this range.[198] If maximum tolerated statin therapy does not lower non–HDL-C below goal levels in patients with triglycerides 200 to 499 mg/dL, adding an agent that primarily lowers triglycerides and VLDL-C may help to achieve atherogenic cholesterol goals. Subgroup analyses from cardiovascular outcome studies provide suggestive evidence of reduced ASCVD event risk with the addition of a triglyceride-lowering agent to statin therapy, particularly in patients with the combination of elevated triglycerides and low HDL-C.[313–316]

Statin intolerance and side effects

Symptoms reported with statin use include mainly muscle-related complaints (myalgias), although there have been some anecdotal reports of short-term memory impairment.[122,317,318] Observational studies have failed to find significant evidence for memory loss in those on longer-term statin therapy. It is important to remember that musculoskeletal complaints are common in elderly patients without statin therapy, so an evaluation of such complaints to assess other possible causes should be undertaken before attributing such symptoms to statin therapy. It is also common for patients to have concomitant therapies with the potential to interact with statins, increasing the risk of muscle symptoms.[319,320] For patients with statin intolerance, symptoms may improve when the patient is switched to a different statin. Other strategies that may be used include limiting the daily dosage and modified regimens such as every other day or once weekly dosing with statins that have a long half-life. In some patients, it may be possible to switch to an alternative concomitant therapy to enhance statin tolerance. For patients who cannot tolerate a statin with the previously discussed strategies, a nonstatin drug alone or in combination with another cholesterol-lowering agent may be considered.[321]

A modest increase in risk for type 2 diabetes mellitus has been observed with stain therapy in RCTs, and higher intensity statin therapy appears to increase risk to a greater extent than less-intensive regimens.[322–324] The increase in

diabetes incidence seems to occur mainly in those with diabetes risk factors, such as the metabolic syndrome components.[324,325] However, these analyses also suggest that several ASCVD events are prevented for each excess case of diabetes produced by statin therapy, or higher intensity statin therapy. Therefore, the panel recommends that fasting glucose or glycated hemoglobin be checked before initiation of statin therapy and within 1 year afterward in those with diabetes risk factors.[324] In addition, lifestyle therapies should be emphasized, both to aid in lowering levels of atherogenic cholesterol and for reducing diabetes risk.

Combination drug therapy

Therapy with a statin plus a second (or third) agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in patients with very high or high risk.[321] The maximum tolerated statin dosage should generally be used before add-on therapy is considered. A meta-analysis of data from RCTs of statin use demonstrated a large interindividual variability in the reduction of LDL-C, non–HDL-C, and apo B (Fig. 7).[97] Among those patients treated with high-dose statin therapy, more than 40% did not reach their LDL-C target of <70 mg/dL. This demonstrates that statin therapy alone may be insufficient for some individuals to reach goal and supports the recommendation to consider combination drug therapy.

The nonstatin drug classes are generally safe, and there is RCT evidence for ASCVD reduction associated with the use of niacin, gemfibrozil, and cholestyramine as monotherapies.[4,84,85,301–303] However, results from the Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study of extended release niacin with laropiprant indicated that in addition to expected side effects of skin irritation and gastrointestinal disturbance, niacin also increased myopathy among patients in China and increased risk for other unexpected side effects including bleeding and infections.[216] Several nonstatins also have RCT evidence for ASCVD reduction as statin adjuncts in subgroup analyses of patients with elevated triglycerides or elevated triglycerides plus low HDL-C concentrations.[198] These include eicosapentaenoic acid ethyl esters,[313,326] fibrates (Fig. 14),[314,327] and niacin.[213,315]

Ezetimibe, an NPC1L1 protein inhibitor that reduces cholesterol absorption, has been shown to produce significant additional improvements in LDL-C levels and goal attainment when added to statin therapy.[328] The efficacy of ezetimibe as add-on therapy to a statin after acute coronary syndromes in 18,444 patients was evaluated in the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).[83,329] At the time of this writing, the results from IMPROVE-IT were not published, but based on a presentation of the data at the American Heart Association 2014 Scientific Sessions, 7-year event rates showed that 32.7% of patients treated with ezetimibe plus simvastatin had the primary outcome of cardiovascular
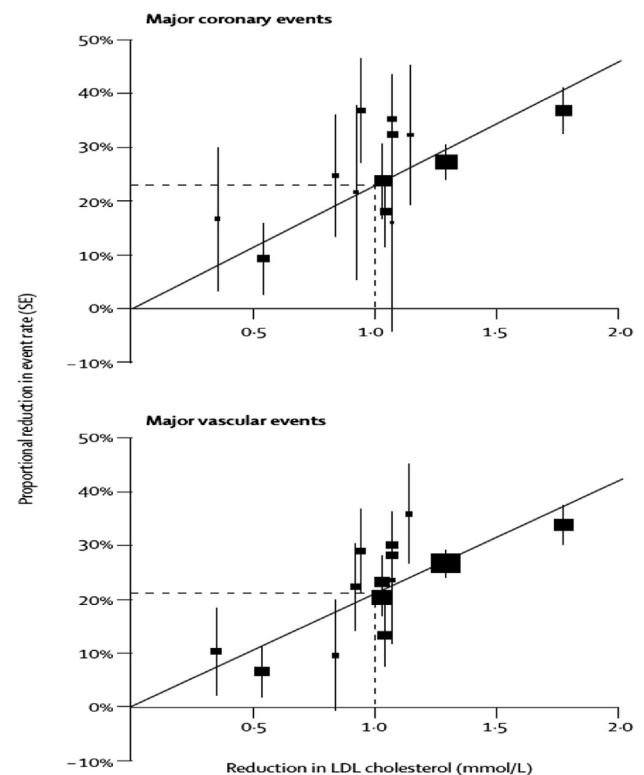

Figure 15 Relation between proportional reduction in incidence of major coronary events and major vascular events and mean absolute low-density lipoprotein (LDL) cholesterol reduction.[92] Square represents a single trial plotted against mean absolute LDL cholesterol reduction at 1 year, with vertical lines above and below corresponding to one standard error of unweighted event rate reduction. Trials are plotted in order of magnitude of difference in LDL cholesterol difference at 1 year. For each outcome, regression line (which is forced to pass through the origin) represents weighted event rate reduction per mmol/L LDL cholesterol reduction. Taken from Baigent C et al.[92]

death, myocardial infarction, documented unstable angina requiring hospitalization, coronary revascularization, or stroke compared with 34.7% of subjects treated with simvastatin alone (hazard ratio, 0.936; confidence interval, 0.887–0.988; P = .016).[83] Median LDL-C levels at 1 year were 53.2 mg/dL with ezetimibe plus simvastatin vs 69.9 mg/dL with simvastatin alone. The results for ezetimibe as a statin add-on are consistent with effects predicted from studies of the intensification of statin therapy. According to the reported relationship of a 22% reduction in major vascular events per 1 mmol/L reduction in LDL-C from statin therapies (Fig. 15),[92,98] the predicted reduction in major vascular events with combination therapy in IMPROVE-IT would be 9.5%, which is nearly identical to the reported reduction of 10%.[83] The number needed to treat for prevention of the primary end point was 50, calculated using 7-year event rates, the median follow-up in the trial. Thus, assuming no off-target effects, these results suggest that the manner in which atherogenic cholesterol levels are lowered does not alter the magnitude of ASCVD risk reduction

Table 14   LDL apheresis[*]

NLA criteria from Expert Panel on FH	FDA-approved indication
LDL apheresis may be considered for the following patients who, after 6 mo, do not have adequate response to maximum tolerated drug therapy: • Functional homozygous FH with LDL-C ≥300 mg/dL (or non–HDL-C ≥330 mg/dL) • Functional heterozygous FH with LDL-C ≥300 mg/dL (or non–HDL-C ≥330 mg/dL) and 0 to 1 risk factors • Functional heterozygous FH with LDL-C ≥200 mg/dL (or non–HDL-C ≥230 mg/dL) and high risk characteristics, such as 2 risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform-insensitive assay • Functional heterozygous FH with LDL-C ≥160 mg/dL (or non–HDL-C ≥190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes)	LDL apheresis is considered medically necessary when patients have failed diet and maximum drug therapy from at least 2 separate classes of hypolipidemic drugs for at least 6 mo in addition to any 1 of the following criteria: • Homozygous FH with LDL-C ≥500 mg/dL • Heterozygous FH with LDL-C ≥300 mg/dL • Functional heterozygous FH with LDL-C ≥200 mg/dL in patients with coronary artery disease

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

*The NLA criteria[253,337] are more inclusive than the FDA-approved indication criteria. Clinicians should be aware of this with regard to reimbursement.

and support the benefits of lowering atherogenic cholesterol to levels below 70 mg/dL.

Much of the available data for the effects of add-on therapy on ASCVD events are from RCTs in which add-on therapy was administered to patients with relatively low levels of atherogenic cholesterol during statin treatment.[330] These studies therefore did not adequately test the hypothesis that adding another lipid-altering therapy to maximum statin therapy would reduce ASCVD risk among patients still above their atherogenic cholesterol goal. In the Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial, patients had a mean LDL-C level of <70 mg/dL before the addition of niacin to statin.[213] Similarly, LDL-C level before adding niacin + laropiprant to statin in HPS2-THRIVE was very low—approximately 64 mg/dL,[216] as was the LDL-C level (∼100 mg/dL) in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study of fenofibrate added to statin therapy.[314] Thus, limited RCT evidence is available to guide therapy in the patient taking the highest tolerated dosage of a statin, whose levels of atherogenic cholesterol remain above treatment goals.

Observational data as well as results from RCTs comparing lower and higher intensity statin therapy suggest that ASCVD event risk is associated with levels of atherogenic cholesterol and that larger reductions in atherogenic cholesterol levels, or lower on-treatment levels, are associated with greater ASCVD event benefits.[4,8,97,173] The association between on-treatment levels of LDL-C (and non–HDL-C) appears to follow a log-linear relationship, which is consistent with the view that the primary mechanism of action of statins is through reductions in levels of atherogenic lipoproteins, reflected by lower levels of circulating concentrations of atherogenic cholesterol.[8,20,97] Moreover, results from studies of different approaches to

cholesterol lowering suggest that the degree of risk reduction with statin therapy for a given reduction in atherogenic cholesterol is similar to that observed with other cholesterol-lowering interventions, including other medications, diet, and ileal bypass surgery.[8,37,173] However, potential off-target effects of statin and nonstatin drugs should also be considered when evaluating their potential to alter risk for ASCVD.[331,332]

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

Treatment of patients with severe hypercholesterolemia

Patients with the severe hypercholesterolemia phenotype (LDL-C, ≥190 mg/dL), if untreated, have markedly elevated lifetime risk for ASCVD, particularly premature ASCVD.[253,256] Many such patients have FH, an autosomal codominant (monogenic) form of hypercholesterolemia resulting from reduced expression of LDL receptors.[54,55] Other forms of severe hypercholesterolemia result from production of defective apo B that does not have normal interactivity with hepatic LDL receptors and from gain-of-function mutations in the PCSK9 gene.[54]

In some patients with severe hypercholesterolemia, it may not be possible to achieve goal levels of atherogenic

Chart 4   Recommendations for application of lifestyle and drug therapies intended to reduce morbidity and mortality associated with dyslipidemia

Recommendations	Strength	Quality
For patients at low or moderate risk, lifestyle therapy should be given a trial of at least 3 mo before initiation of drug therapy.	E	Moderate
For patients at very high risk and selected patients at high risk (those unlikely to reach goal with lifestyle alone), drug therapy may be started concurrently with lifestyle therapy.	E	Low
Referral to an RDN is recommended to facilitate dietary modification and to an exercise specialist for guided instruction on a suitable exercise program.	A	Moderate
Dietary adjuncts including plant sterols and stanols and viscous fibers can be considered for use by patients when sufficient progress is not made toward achieving atherogenic cholesterol goals with initial lifestyle therapies.	B	Moderate
After atherogenic cholesterol targets are achieved with lifestyle therapies, responses should continue to be monitored at intervals of 6–12 mo.	E	Low
Before initiation of atherogenic cholesterol–lowering drug therapy, the clinician should discuss with the patient the treatment objectives, potential adverse effects, possible interactions with other drugs or dietary supplements, lifestyle and medication adherence, and patient preferences as well as convey that alternative agents and regimens are available in the event of side effects.	E	Low
Clinicians may prefer to prescribe drug therapy (mainly statins) to patients with lower levels of risk or atherogenic cholesterol than outlined by the NLA Expert Panel, based on clinical judgment and patient preferences.	E	Low
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.	A	High
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.	A	High
Combination drug therapy with a statin plus a second (or third) agent that further lowers non–HDL-C and LDL-C may be considered for patients who have not attained their atherogenic cholesterol levels after the maximum tolerated statin dosage has been reached and for those who have contraindications or are intolerant to statin therapy.	A	Moderate
If drug therapy is used, at least a 30% reduction in atherogenic cholesterol should be targeted.	A	Moderate
After atherogenic cholesterol–lowering targets are achieved with drug therapy, response to therapy should be monitored within 4–12 mo.	E	Low
For patients with very high triglycerides (≥500 mg/dL), the primary objective of therapy is to lower the triglyceride level to <500 mg/dL to reduce the risk of pancreatitis.	A	Moderate
For patients with high triglycerides (200–499 mg/dL), the primary objective of therapy is to lower levels of non–HDL-C and LDL-C to reduce risk for an ASCVD event.	B	Low
Lifestyle interventions are key to efforts to reduce triglycerides. When drug therapy is indicated, an agent that primarily lowers triglycerides should be considered for patients with triglycerides ≥1000 mg/dL, a triglyceride-lowering agent or a statin may be reasonable for patients with triglycerides 500–999 mg/dL, and a statin should generally be first-line drug therapy for patients with triglycerides 200–499 mg/dL.	E	Moderate
In patients with statin intolerance, strategies such as limiting the daily dosage and modified regimens may be considered. If the patient still cannot tolerate the statin, a nonstatin drug alone or in combination with another cholesterol-lowering agent may be considered.	E	Moderate
Glucose or glycated hemoglobin should be checked before initiation of statin therapy and within 1 y afterward in those with diabetes risk factors.	E	Moderate
For selected patients with severe hypercholesterolemia, an alternative goal is to lower atherogenic cholesterol levels by at least 50%. LDL apheresis may be considered for selected patients.	B	Moderate
Very aggressive therapy to lower atherogenic cholesterol levels to values well below goal thresholds may be considered for patients with progressive atherosclerosis or recurrent events, despite receiving high-intensity statin therapy. Other potential causes should also be investigated and nonlipid risk factors should be well controlled.	E	Low

cholesterol, even with combination drug therapy. When this is the case, an alternative goal is to lower atherogenic cholesterol levels by at least 50%.[253] New classes of medications (eg, PCSK9 inhibitors) are under investigation that, if shown to be safe and efficacious, may make attainment of goal levels of atherogenic cholesterol practical for a greater fraction of patients with severe hypercholesterolemia.[333,334]

Mipomersen, an injectable antisense inhibitor of apo B synthesis, when given in combination with maximum tolerated doses of lipid-lowering therapy, can reduce LDL-C by an additional 25% in homozygous FH patients, but even the addition of mipomersen does not achieve the recommended LDL-C target in the vast majority of homozygous FH patients.[335] In addition, injection-site reactions, hepatic fat and liver enzyme elevations are common. Lomitapide, an oral inhibitor of microsomal triglyceride transfer protein, can also reduce LDL-C levels by up to 50% in homozygous FH patients on maximum tolerated lipid-lowering therapy and LDL apheresis.[336] However, given its mechanism of action, gastrointestinal side effects and elevation in liver enzymes and hepatic fat are common. Because of the risk of hepatotoxicity, mipomersen and lomitapide are available only through Risk Evaluation and Mitigation Strategy programs.

For selected patients with severe hypercholesterolemia, LDL apheresis may be considered. Table 14 shows the NLA Expert Panel on FH criteria for consideration of LDL apheresis.[253,337] These criteria are more inclusive than the Food and Drug Administration–approved indications, which clinicians should be aware of with regard to reimbursement.

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

Little evidence is available from RCTs to guide treatment of patients with progressive atherosclerosis, or recurrent events, despite receiving high-intensity statin therapy.[94,338-340] The NLA Expert Panel consensus view is that very aggressive therapy to lower atherogenic cholesterol levels to values well below goal thresholds may be considered for such patients, although it is acknowledged that this approach is not clearly supported by clinical trial evidence. Investigation of other potential causes, such as an elevated level of Lp (a) or other additional risk indicators may be warranted in such patients.[341,342] Nonlipid risk factors should be well controlled in such patients. Chart 4 summarizes the recommendations for application of lifestyle and drug therapies intended to reduce morbidity and mortality associated with dyslipidemia.

Updates to this document

Because the evidence in clinical medicine related to lipid management is always evolving, these recom-

mendations will undergo annual review with revision as necessary to reflect important changes to the evidence base.

References

1. Jacobson TA. NLA Task Force on Statin Safety—2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S1–S4.

2. James PA, Oparil S, Carter BL, et al. 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 (JNC 8). *JAMA*. 2014;311:507–520.

3. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B): 2889–2934.

4. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106: 3143–3421.

5. Catapano AL, Reinzer Z, De Backer G, et al, European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS guidelines for the management of dyslipidaemias. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis*. 2011;217:3–46.

6. Jellinger PS, Smith DA, Mehta AE, et al, AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis. American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract*. 2012;18(Suppl 1):1–78.

7. Anderson TJ, Gregoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2013;29:151–167.

8. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia—full report. *J Clin Lipidol*. 2014;8:29–60.

9. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2935–2959.

10. National Institute for Health Care and Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 181. Issued July 2014.

11. American Diabetes Association. Standards of medical care in diabetes—2015. Section 8. Cardiovascular disease and risk management. *Diabetes Care*. 2015;38(Suppl 1):S49–S57.

12. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1—executive summary. *J Clin Lipidol*. 2014;8: 473–488.

13. Guyatt GH, Oxman AD, Vist GE, et al, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.

14. Walsh MN, Bove AA, Cross RR, et al, American College of Cardiology Foundation. ACCF 2012 health policy statement on patient-centered care in cardiovascular medicine: a report of the American College of Cardiology Foundation Clinical Quality Committee. *J Am Coll Cardiol*. 2012;59:2125–2143.

15. Sniderman AD, LaChapelle KJ, Rachon NA, Furberg CD. The necessity for clinical reasoning in the era of evidence-based medicine. *Mayo Clin Proc*. 2013;88:1108–1114.

16. Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: definitions and applications to improve outcomes. *J Am Acad Nurse Pract*. 2008;20:600–607.

17. Calvert SB, Kramer JM, Anstrom KJ, Kaltenbach LA, Stafford JA, Allen LaPointe NM. Patient-focused intervention to improve long-term adherence to evidence-based medications: a randomized trial. *Am Heart J*. 2012;163:657–665.

18. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol*. 2012;6:208–215.

19. Go AS, Mozaffarian D, Roger VL, et al, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update; a report from the American Heart Association. *Circulation*. 2014;129:e28–e292.

20. Grundy SM, Cleeman JI, Merz CN, et al, Coordination Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol*. 2004;44: 720–732.

21. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart*. 2014;100: ii1–ii67.

22. Chung BH, Tallis G, Yalamoori V, Anantharamaiah GM, Segrest JP. Liposome-like particles isolated from human atherosclerotic plaques are structurally and compositionally similar to surface remnants of triglyceride-rich lipoproteins. *Arterioscler Thromb*. 1994;14: 622–635.

23. Rapp JH, Lespine A, Hamilton RL, et al. Triglyceride-rich lipoproteins isolated by selected affinity anti-apolipoprotein B immunoadsorption from human atherosclerotic plaque. *Arterioscler Thromb*. 1994;14:1767–1774.

24. Havel RJ. Remnant lipoproteins as therapeutic targets. *Curr Opin Lipidol*. 2000;11:615–620.

25. Veniant MM, Sullivan MA, Kim SK, et al. Defining the atherogenicity of large and small lipoproteins containing apolipoprotein B100. *J Clin Invest*. 2000;106:1501–1510.

26. Twickler T, Dallinga-Thie GM, Chapman MJ, Cohn JS. Remnant lipoproteins and atherosclerosis. *Curr Atheroscler Rep*. 2005;7: 140–147.

27. Varbo A, Benn M, Tybaerg-Hansen A, Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436.

28. Varbo A, Benn M, Nordestgaard BG. Remnant cholesterol as a cause of ischemic heart disease: evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment. *Pharmacol Ther*. 2014;141:358–367.

29. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.

30. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation*. 1998;97:1029–1036.

31. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med*. 2001;161:1413–1419.

32. Farwell WR, Sesso HD, Buring JE, Gaziano JM. Non-high-density lipoprotein cholesterol versus low-density lipoprotein cholesterol as a risk factor for a first nonfatal myocardial infarction. *Am J Cardiol*. 2005;96:1129–1134.

33. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures,

lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005;294:326–333.

34. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol*. 2006;98:1363–1368.

35. Holme I, Aastveit AH, Jungner I, Walldius G. Relationships between lipoprotein components and risk of myocardial infarction: age, gender and short versus longer follow-up periods in the Apolipoprotein MOrtality RISk study (AMORIS). *J Intern Med*. 2008;264: 30–38.

36. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.

37. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol*. 2009;53: 316–322.

38. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115–126.

39. Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 2007;116:1832–1844.

40. Frostegard J. Immunity, atherosclerosis and cardiovascular disease. *BMC Med*. 2013;11:117.

41. Van Wijk DF, Sjouke B, Figueroa A, et al. Nonpharmacological lipoprotein apheresis reduces arterial inflammation in familial hypercholesterolemia. *J Am Coll Cardiol*. 2014;64:1418–1426.

42. Steinberg D. The LDL modification of atherogenesis: an update. *J Lipid Res*. 2009;50:S376–S381.

43. Wang J, Razuvaev A, Folkersen L, et al. The expression of IGFs and IGF binding proteins in human carotid atherosclerosis, and the possible role of IGF binding protein-1 in the regulation of smooth muscle cell proliferation. *Atherosclerosis*. 2012;220:102–109.

44. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J*. 2013;34: 719–728.

45. Libby P. Molecular bases of the acute coronary syndromes. *Circulation*. 1995;91:2844–2850.

46. Libby P, Schoenbeck U, Mach F, Selwyn AP, Ganz P. Current concepts in cardiovascular pathology: the role of LDL cholesterol in plaque rupture and stabilization. *Am J Med*. 1998;104(2A): 14S–18S.

47. Théroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. *Circulation*. 1998;97: 1195–1206.

48. Fuster V, Fayad ZA, Badimon JJ. Acute coronary syndromes: biology. *Lancet*. 1999;353(suppl II):SII5–SII9.

49. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the pooling project. *J Chronic Dis*. 1978;31:201–306.

50. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256:2823–2828.

51. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham Study. *JAMA*. 1987;257: 2176–2180.

52. Anderson KM, Wilson PW, Garrison RJ, Castelli WP. Longitudinal and secular trends in lipoprotein cholesterol measurements in a general population sample. The Framingham Offspring Study. *Atherosclerosis*. 1987;68:59–66.

53. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ*. 1994;308:367–372.

54. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl): S9–S17.

55. Izar MC, Machado VA, Fonseca FA. Genetic screening for homozygous and heterozygous familial hypercholesterolemia. *Appl Clin Genet*. 2010;3:147–157.

56. Cohen JC, Boerwinkle E, Mosley TH Jr., Hoobs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264–1272.

57. Ference BA, Majeed F, Brook RD, Hedquist L, Penumetcha R, Flack JM. Effect of naturally random allocation to lower LDL-C mediated polymorphisms in NPC1L1, HMGCR or both on the risk of coronary heart disease: a 2x2 factorial Mendelian randomization study. *Circulation*. 2014;130:A19754.

58. The Myocardial Infarction Genetics Consortium Investigators. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med*. 2014;371:2072–2082.

59. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb*. 1991;11:2–14.

60. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.

61. Nordestgaard BG, Benn M, Schnohr P, Tybjærg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308.

62. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384:626–635.

63. Freiberg JJ, Tybjærg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152.

64. Chapman MJ, Ginsberg HN, Amarenco P, et al, for the European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;332:1345–1361.

65. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sanghu MS, Ricketts SL, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet*. 2010;374:1634–1639.

66. Johansen CT, Kathiresan S, Hegele RA. Genetic determinants of plasma triglycerides. *J Lipid Res*. 2011;52:189–206.

67. Jorgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated nonfasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*. 2013;34:1826–1833.

68. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BC, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med*. 2014;37:32–41.

69. Hegele RA, Ginsberg HN, Chapman MJ, et al, on behalf of the European Atherosclerosis Society Consensus Panel. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;2: 655–666.

70. Mora S, Buring JE, Ridker PM. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. *Circulation*. 2014;129:553–561.

71. Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. *N Engl J Med*. 1990;323:1112–1119.

72. Gordon DJ. Cholesterol lowering and total mortality. In: Rifkind BM, editor. Lowering cholesterol in high-risk individuals and populations. New York: Marcel Dekker, Inc, 1995. p. 333–348.

73. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of

Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995; 333:1301–1307.

74. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279: 1615–1622.

75. Sever PS, Dahlof B, Poulter NR, et al, ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than average cholesterol concentrations in the ANGLO-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial. *Lancet*. 2003;361:1149–1158.

76. Ridker PM, Danielson E, Fonseca FA, et al, JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.

77. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344: 1383–1389.

78. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med*. 1998;129: 681–689.

79. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339: 1349–1357.

80. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.

81. Pedersen TR, Faergeman O, Kastelein JJ, et al, Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437–2445 Erratum in JAMA 2005;294:3092.

82. LaRosa JC, Grundy SM, Waters DD, et al, Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352: 1425–1435.

83. Cannon CP on behalf of the IMPROVE IT Investigators. IMPROVE-IT Trial: a comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes after acute coronary syndromes. Late-breaking clinical trial abstracts and clinical science special reports abstracts from the American Heart Association's Scientific Sessions 2014. *Circulation*. 2014;130:2105–2126 Presented at AHA 2014. Chicago, IL.

84. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I: Reduction in the incidence of coronary heart disease. *JAMA*. 1984;251:351–364.

85. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365–374.

86. Buchwald H, Varco RL, Boen JR, et al. Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Program on the Surgical Control of the Hyperlipidemias. *Arch Intern Med*. 1998;158:1253–1261.

87. Schwartz GG, Olsson AG, Ezekowitz MD, et al, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;295:1711–1718.

88. Serruys PW, de Feyter P, Macaya C, et al, Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287:3215–3222.

89. Shepherd J, Blauw GJ, Murphy MB, et al, The PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623–1630.

90. Holdaas H, Fellstrom B, Jardine AG, et al, Assessment of Lescol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo controlled trial. *Lancet*. 2003;361:2024–2031.

91. Colhoun HM, Betteridge DJ, Durrington PN, et al, CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696.

92. Baigent C, Keech A, Kearney PM, et al, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.

93. de Lemos JA, Blazing MA, Wiviott SD, et al, for the A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292:1307–1316.

94. Ray KK, Cannon CP, McCabe CH, et al, PROVE IT-TIMI 22 Investigators. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2005;46:1405–1410.

95. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006; 355:549–559.

96. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. *Circulation*. 2011;123:2870–2891.

97. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol*. 2014;64:485–494.

98. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.

99. Lloyd-Jones DM, Hong Y, Labarthe D, et al, on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586–613.

100. Appel LJ, Sacks FM, Carey VJ, et al, OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;294:2455–2464.

101. Brown MS, Goldstein JL. Biomedicine. Lowering LDL—not only how low, but how long? *Science*. 2006;311:1721–1731.

102. McGill HC Jr., McMahan CA, Malcom GT, Oalmann MC, Strong JP, for the PDAY Research Group. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. *Arterioscler Thromb Vasc Biol*. 1997;17:95–106.

103. McGill HC Jr., McMahan CA. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Determinants of atherosclerosis in the young. *Am J Cardiol*. 1998;82:30T–36T.

104. McGill HC Jr., McMahan CA, Zieske AW, et al. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. *Arterioscler Thromb Vasc Biol*. 2000;20:1998–2004.

105. Klag MJ, Ford DE, Mead LA, et al. Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med*. 1993;328: 313–318.

106. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA*. 2000;284:311–318.

107. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423.

108. Keys A, editor. Seven countries: a multivariate analysis of death and coronary heart disease. Cambridge, Massachusetts: Harvard University Press, 1980.

109. Keys A, Menotti A, Aravanis C, et al. The seven countries study: 2,289 deaths in 15 years. *Prev Med*. 1984;13:141–154.

110. Packard CJ, Ford I, Murray H, McCowan C. Lifetime clinical and economic benefits of statin-based LDL lowering in the 20-year follow-up of the West of Scotland Coronary Prevention Study. Late-breaking clinical trial abstracts and clinical science special reports abstracts from the American Heart Association's Scientific Sessions 2014. *Circulation*. 2014;130:2105–2126 Presented at AHA 2014. Chicago, IL.

111. Toth PP, Thanassoulis G, Williams J, Furberg CD, Sniderman A. The risk-benefit paradigm vs the causal exposure paradigm: LDL as a primary cause of vascular disease. *J Clin Lipidol*. 2014;8:594–605.

112. Brown BG, Zhao XQ. Lipid therapy to stabilize the vulnerable atherosclerotic plaque: new insights into the prevention of cardiovascular events. In: Grundy SM, editor. Cholesterol-lowering therapy: evaluation of clinical trial evidence. New York: Marcel Dekker, 2000.

113. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–798.

114. Pencina MJ, D'Agostino RB Sr., Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:3078–3084.

115. Choi J, Daskalopoulou SS, Thanassoulis G, et al, GENESIS-PRAXY Investigators. Sex- and gender-related risk factor burden in patients with premature acute coronary syndrome. *Can J Cardiol*. 2014;30:109–117.

116. Cholesterol Treatment Trialists' Collaboration, Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590.

117. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? *J Am Coll Cardiol*. 2005;46:1855–1862.

118. Ma S, Ma CC. Recent development in pleiotropic effects of statins on cardiovascular disease through regulation of transforming growth factor-beta superfamily. *Cytokine Growth Factor Rev*. 2011;22:167–175.

119. Porter KE, Turner NA. Statins and myocardial remodelling: cell and molecular pathways. *Expert Rev Mol Med*. 2011;13:e22.

120. Davignon J. Pleiotropic effects of pitavastatin. *Br J Clin Pharmacol*. 2012;73:518–535.

121. Mihos CG, Pineda AM, Santana O. Cardiovascular effects of statins, beyond lipid-lowering properties. *Pharmacol Res*. 2014;88:12–19.

122. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S72–S81.

123. Ahmed S, Cannon CP, Murphy SA, Braunwald E. Acute coronary syndromes and diabetes: is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. *Eur Heart J*. 2006;27:2323–2329.

124. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. *Eur Heart J*. 2013;34:2444–2452.

125. Bangalore S, Fayyad R, Laskey R, et al, Treating to New Targets Steering Committee and Investigators. Lipid lowering in patients with treatment-resistant hypertension: an analysis from the Treating to New Targets (TNT) trial. *Eur Heart J*. 2014;35:1801–1808.

126. Green JB. Understanding the type 2 diabetes mellitus and cardiovascular disease risk paradox. *Postgrad Med*. 2014;126:190–204.

127. Yusuf S, Hawken S, Ounpuu S, et al, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART Study): case-control study. *Lancet*. 2004;364:937–952.

128. Skoumas I, Masoura C, Pitsavos C, et al. Evidence that non-lipid cardiovascular risk factors are associated with high prevalence of coronary artery disease in patients with heterozygous familial hypercholesterolemia or familial combined hyperlipidemia. *Int J Cardiol*. 2007;12:178–183.

129. Skoumas I, Masoura C, Aznaouridis K, et al. Impact of cardiometabolic risk factors on major cardiovascular events in patients with familial combined hyperlipidemia. *Circ J*. 2013;77:163–168.

130. González-Pacheco H, Vargas-Barrón J, Vallejo M, et al. Prevalence of conventional risk factors and lipid profiles in patients with acute coronary syndrome and significant coronary disease. *Ther Clin Risk Manag*. 2014;10:815–823.

131. Russo GT, Giandalia A, Romeo EL, et al. Lipid and non-lipid cardiovascular risk factors in postmenopausal type 2 diabetic women with and without coronary heart disease. *J Endocrinol Invest*. 2014;37:261–268.

132. Ray KK, Seshasi SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. *Lancet*. 2009;373:1765–1772.

133. Mannucci E, Dicembrini I, Lauria A, Pozzilli P. Is glucose control important for prevention of cardiovascular disease in diabetes? *Diabetes Care*. 2013;36(suppl 2):S259–S263.

134. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(Suppl 1):S14–S80.

135. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779–785.

136. de Lorgeril M. Mediterranean diet and cardiovascular disease: historical perspective and latest evidence. *Curr Atheroscler Rep*. 2013;15:370.

137. Estruch R, Ros E, Salas-Salvado J, et al, the PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279–1290.

138. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med*. 2000;343:16–22.

139. Hu FB, Willett WC. Diet and coronary heart disease: findings from the Nurses' Health Study and Health Professionals' Follow-up Study. *J Nutr Health Aging*. 2001;5:132–138.

140. Mozaffarian D, Hao T, Rimm EB, Willet WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med*. 2011;364:2392–2404.

141. Stine NW, Chokshi DA. Elimination of lipid levels from quality measures. Implications and alternatives. *JAMA*. 2014;312:1971–1972.

142. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. *J Clin Lipidol*. 2013;7:472–483.

143. Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long-term medication adherence. A study of the dynamics of statin use. *Arch Intern Med*. 2007;167:847–852.

144. Simpson RJ, Mendys P. The effect of adherence and persistence on clinical outcomes in patients treated with statins: a systematic review. *J Clin Lipidol*. 2010;4:462–471.

145. Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density

lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310:2061–2068.

146. Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: The Strong Heart Study. *Diabetes Care*. 2003;26:16–23.

147. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation*. 2005;112:3375–3383.

148. Rallidis LS, Pitsavos C, Panagiotakos DB, Sinos L, Stefanadis C, Kremastinos DT. Non-high density lipoprotein cholesterol is the best discriminator of myocardial infarction in young individuals. *Atherosclerosis*. 2005;179:305–309.

149. Blaha MJ, Blumenthal RS, Brinton EA, Jacobson TA. National Lipid Association Taskforce on Non-HDL Cholesterol. The importance of non-HDL cholesterol in reporting in lipid management. *J Clin Lipidol*. 2008;2:267–273.

150. Arsenault BJ, Rana JS, Stroes ES, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. *J Am Coll Cardiol*. 2009;55:35–41.

151. Mahajan N, Ference BA, Arora N, et al. Role of non-high-density lipoprotein cholesterol in predicting cerebrovascular events in patients following myocardial infarction. *Am J Cardiol*. 2012;109:1694–1699.

152. Kastelein JJ, van der Steeg WA, Holme I, et al, TNT Study Group; IDEAL Study Group. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*. 2008;117:3002–3009.

153. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA*. 2012;307:1302–1309.

154. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009;119:931–939.

155. Ballantyne CM, Raichlen JS, Cain VA. Statin therapy alters the relationship between apolipoprotein B and low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol targets in high-risk patients: the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin) trial. *J Am Coll Cardiol*. 2008;52:56–63.

156. Grundy SM, Vega GL, Tomassini JE, Tershakovec AM. Correlation of non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol with apolipoprotein B during simvastatin + fenofibrate therapy in patients with combined hyperlipidemia (a subanalysis of the SAFARI trial). *Am J Cardiol*. 2009;104:548–553.

157. Grundy SM, Vega GL, Tomassini JE, Tershakovec AM. Comparisons of apolipoprotein B levels estimated by immunoassay, nuclear magnetic resonance, vertical auto profile, and non-high-density lipoprotein cholesterol in subjects with hypertriglyceridemia (SAFARI Trial). *Am J Cardiol*. 2011;108:40–46.

158. Zheng C, Khoo C, Ikewaki K, Sacks FM. Rapid turnover of apolipoprotein C-III-containing triglyceride-rich lipoproteins contributing to formation of LDL subfractions. *J Lipid Res*. 2007;48:1190–1203.

159. Napolitano M, Botham KM, Bravo E. Postprandial human triglyceride-rich lipoproteins increase chemoattractant protein secretion in human macrophages. *Cytokine*. 2013;63:18–26.

160. Frost PH, Havel RJ. Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol*. 1998;81:26B–31B.

161. Davidson MH, Ballantyne CM, Jacobson TA, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an Expert Panel of lipid specialists. *J Clin Lipidol*. 2011;5:338–367.

162. Jacobson TA. 'Trig-onometry': non-high-density lipoprotein cholesterol as a therapeutic target in dyslipidaemia. *Int J Clin Pract*. 2011;65:82–101.

163. Nauck M, Warnick GR, Rifai N. Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation. *Clin Chem*. 2002;48:236–254.

164. Bairaktari ET, Seferiadis KI, Elisaf MS. Evaluation of methods for the measurement of low-density lipoprotein cholesterol. *J Cardiovasc Pharmacol Ther*. 2005;10:45–54.

165. Agrawal M, Spencer HJ, Faas FH. Method of LDL cholesterol measurement influences classification of LDL cholesterol treatment goals: clinical research study. *J Investig Med*. 2010;58:945–949.

166. Yamada K, Tsuji N, Fujita T, et al. Comparison of four direct homogeneous methods for the measurement of low-density lipoprotein cholesterol. *Clin Lab*. 2010;56:327–333.

167. Baruch L, Chiong VJ, Agarwal S, Gupta B. Discordance of non-HDL and directly measured LDL cholesterol: which lipid measure is preferred when calculated LDL is inaccurate? *Cholesterol*. 2013;2013:502948.

168. De Vries M, Klop B, Cabezas MC. The use of the non-fasting lipid profile for lipid-lowering therapy in clinical practice—point of view. *Atherosclerosis*. 2014;234:473–475.

169. Kathiresan S. A PCSK9 missense variant associated with a reduced risk of early-onset myocardial infarction. *N Engl J Med*. 2008;358:2299–2300.

170. Pollin T, Damcott CM, Shen H, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. *Science*. 2008;322:1702–1705.

171. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60:2631–2639.

172. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, Auer PL, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31.

173. Robinson JG, Wang S, Jacobson TA. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. *Am J Cardiol*. 2012;110:1468–1476.

174. Ramjee V, Sperling LS, Jacobson TA. Non-high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification: do the math. *J Am Coll Cardiol*. 2011;58:457–463.

175. Ito MK, Delucca GM, Aldridge MA. The relationship between low-density lipoprotein cholesterol goal attainment and prevention of coronary heart disease-related events. *J Cardiovasc Pharmacol Ther*. 2001;6:129–135.

176. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H. Safety and efficacy of atorvastatin-induced very low-density lipoprotein cholesterol levels in patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). *Am J Cardiol*. 2007;100:747–752.

177. Cannon CP, Braunwald E, McGabe CH, et al. Pravastatin or Atorvastatin Evaluation and infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504 Erratum in N Engl J Med. 2006;354:778.

178. Cannon CP. The IDEAL cholesterol: lower is better. *JAMA*. 2005;294:2492–2494 Erratum in JAMA. 2005;294:2973.

179. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48:438–445.

180. Lipid Research Clinics Program Epidemiology Committee. Plasma lipid distributions in selected North American populations: the Lipid Research Clinics Program Prevalence Study. *Circulation*. 1979;60:427–439.

181. Elshazly MB, Martin SS, Blaha MJ, et al. Non-high-density lipoprotein cholesterol, guideline targets, and population percentiles for secondary prevention in 1.3 million adults. *J Am Coll Cardiol*. 2013;62:1960–1965.

182. Sniderman AD, St-Pierre AC, Cantin B, Dagenais GR, Gespres JP, Lamarche B. Concordance/discordance between plasma apolipoprotein B levels and the cholesterol indexes of atherosclerotic risk. *Am J Cardiol*. 2003;91:1173–1177.

183. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—implications for LDL management. *J Clin Lipidol*. 2007;1:583–592.

184. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011;5:105–113.

185. Martin SS, Michos ED. Are we moving towards concordance on the principle that lipid discordance matters? *Circulation*. 2014;129:539–541.

186. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51:1512–1524.

187. Harper CR, Jacobson TA. Using apolipoprotein B to manage dyslipidemic patients: time for a change? *Mayo Clin Proc*. 2010;85:440–445.

188. AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices, Cole TG, Contois JH, Csako G, et al. Association of apolipoprotein B and nuclear magnetic resonance spectroscopy-derived LDL particle number with outcomes in 25 clinical studies: assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on Best Practices. *Clin Chem*. 2013;59:752–770.

189. Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. *Am Heart J*. 2006;151:975.e1–975.e9.

190. Ballantyne CM, Pitt B, Loscalzo J, Cain VA, Raichlen JS. Alteration of relation of atherogenic lipoprotein cholesterol to apolipoprotein B by intensive statin therapy in patients with acute coronary syndrome (from the Limiting UNdertreatment of lipids in ACS With Rosuvastatin [LUNAR] Trial). *Am J Cardiol*. 2013;111:506–509.

191. Farnier M, Chen E, Johnson-Levonas AO, Sisk CM, Mitchel YB. Effects of extended-release niacin/laropiprant, simvastatin, and the combination of correlations between apolipoprotein B, LDL cholesterol, and non-HDL cholesterol in patients with dyslipidemia. *Vasc Health Risk Manag*. 2014;10:279–290.

192. Witte DR, Taskinen MR, Perttunen-Nio H, Van Tol A, Livingstone S, Colhoun HM. Study of agreement between LDL size and measured by nuclear magnetic resonance and gradient gel electrophoresis. *J Lipid Res*. 2004;45:1069–1076.

193. Ensign W, Hill N, Heward CB. Disparate LDL phenotypic classification among 4 different methods assessing LDL particle characteristics. *Clin Chem*. 2006;52:1722–1727.

194. Sninsky JJ, Rowland CM, Baca AM, Caulfield MP, Superko HR. Classification of LDL phenotypes by 4 methods of determining lipoprotein particle size. *J Investig Med*. 2013;61:942–949.

195. Assmann G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. *Eur Heart J*. 1998;19(Suppl M):M8–M14.

196. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81:7B–12B.

197. Miller M, Stone NJ, Ballantyne C, et al, American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123:2292–2333.

198. Maki K, Bays H, Dicklin M. Treatment options for the management of hypertriglyceridemia: strategies based on the best-available evidence. *J Clin Lipidol*. 2012;6:413–426.

199. Gower RM, Wu H, Foster GA, et al. CD11c/CD18 expression is upregulated on blood monocytes during hypertriglyceridemia and enhances adhesion to vascular cell adhesion molecule-1. *Arterioscler Thromb Vasc Biol*. 2011;31:160–166.

200. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.

201. Ewald N, Hardt PD, Kloer HU. Severe hypertriglyceridemia and pancreatitis: presentation and management. *Curr Opin Lipidol*. 2009;20:497–504.

202. Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. *JAMA Intern Med*. 2013;173:162–164.

203. Lederle F, Bloomfield H. Drug treatment of asymptomatic hypertriglyceridemia to prevent pancreatitis: where is the evidence? *Ann Intern Med*. 2012;157:662–665.

204. Preiss D, Tikkanen MJ, Welsh P, et al. Lipid-modifying therapies and risk of pancreatitis. A meta-analysis. *JAMA*. 2012;308:804–811.

205. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation*. 1989;79:8–15.

206. Fruchart JC, Sacks F, Hermans MP, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol*. 2008;102:1K–34K.

207. Teramoto T, Sasaki J, Ishibashi S, et al. Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan – 2012 Version. *J Atheroscler Thromb*. 2013;20:517–523.

208. Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: current and future therapies. *J Am Coll Cardiol*. 2010;55:1283–1299.

209. Barter P. HDL-C: role as a risk modifier. *Atheroscler Suppl*. 2011;12:267–270.

210. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomized controlled trials including 117,411 patients. *BMJ*. 2014;349:g4379.

211. Stefanutti C, Labbadia G, Athyros VG. Hypertriglyceridaemia, postprandial lipaemia and non-HDL cholesterol. *Curr Pharm Des*. 2014;20:6238–6248.

212. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomization study. *Lancet*. 2012;380:572–580.

213. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267 Correction in N Engl J Med. 2012;367:189.

214. Schwartz GG, Olsson AG, Abt M, et al, dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089–2099.

215. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 24,673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34: 1279–1291.

216. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371:203–212.

217. Kaur N, Pandey A, Negi H, et al. Effect of HDL-raising drugs on cardiovascular outcomes: a systematic review and meta-regression. *PLoS One*. 2014;9:e94585.

218. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med*. 2006;119: 812–819.

219. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death. *J Am Coll Cardiol*. 2007; 49:403–414.

220. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk. A systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132.

221. Tenenbaum A, Fisman EZ. "The metabolic syndrome…is dead": these reports are an exaggeration. *Cardiovasc Diabetol*. 2011;10:11.

222. Ma X, Zhu S. Metabolic syndrome in the prevention of cardiovascular diseases and diabetes—still a matter of debate? *Eur J Clin Nutr*. 2013;67:518–521.

223. Shin JA, Lee JH, Lim SY, et al. Metabolic syndrome as a predictor of type 2 diabetes, and its clinical interpretations and usefulness. *J Diabetes Investig*. 2013;4:334–343.

224. Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract*. 2014;2014:943162.

225. Dod HS, Bhardwaj R, Sajja V, et al. Effect of intensive lifestyle changes on endothelial function and on inflammatory markers of atherosclerosis. *Am J Cardiol*. 2010;105:362–367.

226. Bays HE, Toth PP, Kris-Etherton PM, et al. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *J Clin Lipidol*. 2013;7:304–383.

227. Voeghtly LM, Neatrour DM, Decewicz DJ, et al. Cardiometabolic risk reduction in an intensive cardiovascular health program. *Nutr Metab Cardiovasc Dis*. 2013;23:662–669.

228. Wang Y, Yu Q, Chen Y, Cao F. Pathophysiology and therapeutics of cardiovascular disease in metabolic syndrome. *Curr Pharm Des*. 2013;19:4799–4805.

229. Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *Am J Clin Nutr*. 2002;76:743–749.

230. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr*. 2004;79:379–384.

231. Roopakala MS, Suresh A, Ashtalakshmi, et al. Anthropometric measurements as predictors of intraabdominal fat thickness. *Indian J Physiol Pharmacol*. 2009;53:259–264.

232. Einhorn D, Reaven GM, Cobin RH, et al, American College of Endocrinology Task Force on the Insulin Resistance Syndrome. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9:236–252.

233. Cheal KL, Abbasi F, Lamendola C, McLaughlin R, Reaven GM, Ford ES. Relationship to insulin resistance of the Adult Treatment Panel III diagnostic criteria for identification of the metabolic syndrome. *Diabetes*. 2004;53:1195–1200.

234. Ryan MC, Farin MF, Abbasi F, Reaven GM. Comparison of waist circumference versus body mass index in diagnosing metabolic syndrome and identifying apparently healthy subjects at increased risk of cardiovascular disease. *Am J Cardiol*. 2008; 102:40–46.

235. Ford ES, Li C, Zhao G, Tsai J. Trends in obesity and abdominal obesity among adults in the United States from 1999-2008. *Int J Obes*. 2011;35:736–743.

236. Bozeman SR, Hoaglin DC, Burton TM, Pashos CL, Ben-Joseph RH, Hollenbeak CS. Predicting waist circumference from body mass index. *BMC Med Res Methodol*. 2012;12:115.

237. Stone NJ. Secondary causes of hyperlipidemia. *Med Clin North Am*. 1984;78:117–141.

238. Mantel-Teeuwisse AK, Kloosterman JME, Maitland-van der Zee AH, Klungel OH, Porsius AJ, de Boer A. Drug-induced lipid changes. A review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Saf*. 2001;24:443–456.

239. Meyer JM. Novel antipsychotics and severe hyperlipidemia. *J Clin Psychopharmacol*. 2001;21:369–374.

240. Correll CU, Fredrickson AM, Kane JM, Manu P. Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. *J Clin Psychiatry*. 2006; 67:575–583.

241. Wiggins BS, Saseen JJ, Spinler SA, editors. Pharmacist's guide to lipid management. Lenexa, KS: American College of Clinical Pharmacy, 2008.

242. Tziomalos K, Athuros VG, Karagiannis A, Mikhailidis DP. Dyslipidemia induced by drugs used for the prevention and treatment of vascular diseases. *Open Cardiovasc Med J*. 2011;5:85–89.

243. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. *Am J Cardiol*. 2012;110:823–825.

244. Ito MK. Chapter 12. Dyslipidemias. In: Chisolm-Burns M, Schwinghammer T, Wells B, Malone P, DiPiro J, editors. Pharmacotherapy principles & practice. 3rd ed. Blacklick, OH: McGraw-Hill Education, 2013.

245. Al-Delaimy WK, Manson JE, Solomon CG, et al. Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. *Arch Intern Med*. 2002;162:272–279.

246. Al-Delaimy WK, Stampfer MJ, Manson JE, Willett WC. Toenail nicotine levels as predictors of coronary heart disease among women. *Am J Epidemiol*. 2008;167:1342–1348.

247. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.

248. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107: 363–369.

249. Ridker PM, Bassuk SS, Toth PP. C-reactive protein and risk of cardiovascular disease: evidence and clinical application. *Curr Atheroscler Rep*. 2003;5:341–349.

250. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004;291: 210–215.

251. Greenland P, Bonow RO, Brundage BH, et al, American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computer Tomography); Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computer Tomograph. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computer tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computer Tomography). *Circulation*. 2007;115:402–426.

252. Nordestgaard BG, Chapman MJ, Ray K, et al, European Atherosclerosis Society Consensus Panel. Lipoprotein (a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31: 2844–2853.

253. Ito MK, McGowan MP, Moriarty PM, National Lipid Association Expert Panel on Familial Hypercholesterolemia. Management of familial hypercholesterolemias in adult patients: recommendations

from the National Lipid Association Expert Panel on familial hyper-cholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl):S38–S45.

254. Cox LA Jr. Low-dose nonlinear effects of smoking on coronary heart disease risk. *Dose Response*. 2012;10:219–232.

255. KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3: 136–150.

256. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. *J Am Coll Cardiol*. 2014;63:1935–1947.

257. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Circulation*. 2014;130:1110–1130.

258. Livingstone SJ, Levin D, Looker HC, et al, Scottish Diabetes Research Network epidemiology group; Scottish Renal Registry. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. *JAMA*. 2015;313:37–44.

259. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998; 32(suppl 3):S112–S119.

260. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.

261. Wanner C, Krane V, Marz W, et al, German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–248.

262. Baigent C, Landray MJ, Reith C, et al, SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011; 377:2181–2192.

263. Barylski M, Nikfar S, Mikhailidis DP, et al, Lipid and Blood Pressure Meta-Analysis Collaboration Group. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy—a meta-analysis of 11 randomized controlled trials involving 21,295 participants. *Pharmacol Res*. 2013;72:35–44.

264. Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J*. 2013;34: 1807–1817.

265. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297:611–619.

266. Nakamura H, Arakawa K, Itakura H, et al, MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet*. 2006;368:1155–1163.

267. Lackland DT, Elkind MS, D'Agostino R Sr., et al, American Heart Association Stroke Council; Council on Epidemiology and Prevention; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research Inclusion of stroke in cardiovascular risk prediction instruments: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2012;43:1998–2027.

268. Amin NP, Martin SS, Blaha MJ, Nasir K, Blumenthal RS, Michos ED. Headed in the right direction but at risk for miscalculation: a critical appraisal of the 2013 ACC/AHA Risk Assessment Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt A):2789–2794.

269. Brown WV, Bittner VA, McKenney JM, Ziajka PE. JCL Roundtable: lipid-lowering drugs in those older than 75 years of age. *J Clin Lipidol*. 2014;8:533–541.

270. Muntner P, Colantonio LD, Cushman M, et al. Validation of the Atherosclerotic Cardiovascular Disease Pooled Cohort Risk Equations. *JAMA*. 2014;311:1406–1415.

271. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet*. 2013;383:1762–1765.

272. Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator. The roles of statins, revascularization, and underascertainment in the Women's Health Study. *JAMA Intern Med*. 2014;174: 1964–1971.

273. Kavousi M, Leening MJ, Nanchen D, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA*. 2014; 311:1416–1423.

274. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329.

275. Gamboa CM, Safford MM, Levitan EB, et al. Statin underuse and low prevalence of LDL-C control among U.S. adults at high risk of coronary heart disease. *Am J Med Sci*. 2014;348:108–114.

276. Robinson JG. Contemporary evidence-based guidelines: practice based on the strongest evidence. *Mayo Clin Proc*. 2014;89:1176–1182.

277. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computer tomography. *J Am Coll Cardiol*. 2000;36:1253–1260.

278. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol*. 2005;46:158–165.

279. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med*. 2004;164: 1285–1292.

280. Whelton SP, Nasir K, Blaha MJ, et al. Coronary artery calcium and primary prevention risk assessment: what is the evidence? An updated meta-analysis on patient and physician behavior. *Circ Cardiovasc Qual Outcomes*. 2012;5:601–607.

281. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795.

282. Yeboah J, Carr JJ, Terry JG, et al. Computed tomography-derived cardiovascular risk markers, incident cardiovascular events, and all-cause mortality in nondiabetics: the Multi-Ethnic Study of Atherosclerosis. *Eur J Prev Cardiol*. 2014;21:1233–1241.

283. Budoff MJ, Mohlenkamp S, McClelland R, et al, Multi-Ethnic Study of Atherosclerosis and the Investigator Group of the Heinz Nixdorf RECALL Study. A comparison of outcomes with coronary artery calcium scanning in unselected populations: the Multi-Ethnic Study of Atherosclerosis (MESA) and Heinz Nixdorf RECALL study (HNR). *J Cardiovasc Comput Tomogr*. 2013;7:182–191.

284. Sunkara N, Wong ND, Malik S. Role of coronary artery calcium in cardiovascular risk assessment. *Expert Rev Cardiovasc Ther*. 2014; 12:87–94.

285. Blaha MJ, Silverman MG, Budoff MJ. Is there a role of coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease?: Clinical risk scores are not sufficient to define primary prevention treatment strategies among asymptomatic patients. *Circ Cardiovasc Imaging*. 2014;7: 398–408.

286. Nasir K, Michos ED, Blumenthal RS, Raggi P. Detection of high-risk young adults and women by coronary calcium and National Cholesterol Education Program Panel III guidelines. *J Am Coll Cardiol*. 2005;46:1931–1936.

287. Nasir K, Shaw LJ, Liu ST, et al. Ethnic differences in the prognostic value of coronary artery calcification for all-cause mortality. *J Am Coll Cardiol*. 2007;50:953–960.

288. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008;358:1336–1345.

289. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results

from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2006;113:30–37.

290. deGoma EM, Dunbar RL, Jacoby D, French B. Differences in absolute risk of cardiovascular events using risk-refinement tests: a systematic analysis of four cardiovascular risk equations. *Atherosclerosis*. 2013;227:172–177.

291. Lakoski SG, Greenland P, Wong ND, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med*. 2007;167:2437–2442.

292. Silverman MG, Blaha MJ, Krumholz HM, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. 2014;35:2232–2241.

293. Jebb SA, Ahern AL, Olson AD, et al. Primary care referral to a commercial provider for weight loss treatment versus standard care: a randomised controlled trial. *Lancet*. 2011;378:1485–1492.

294. Jolly K, Lewis A, Beach J, et al. Comparison of range of commercial or primary care led weight reduction programmes with minimal intervention control for weight loss in obesity: Lighten Up randomised controlled trial. *BMJ*. 2011;343:d6500.

295. Cohen JD, Aspry KE, Brown AS, et al. Use of health information technology (HIT) to improve statin adherence and low-density lipoprotein cholesterol goal attainment in high-risk patients: proceedings from a workshop. *J Clin Lipidol*. 2013;7:573–609.

296. Robinson JG. Starting primary prevention earlier with statins. *Am J Cardiol*. 2014;114:1437–1442.

297. Grundy SM. Treatment targets in the management of dyslipidemias: which targets in whom? *Curr Cardiol Rep*. 2012;14:692–700.

298. Grundy SM. Statins for all? *Am J Cardiol*. 2014;114:1443–1446.

299. Jones PH, Davidson MH, Stein EA, et al, STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol*. 2003;92:152–160.

300. Pang J, Chan DC, Watts GF. Critical review of non-statin treatments for dyslipoproteinemia. *Expert Rev Cardiovasc Ther*. 2014;12:359–371.

301. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360–381.

302. Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. *Atherosclerosis*. 2010;210:353–361.

303. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;375:1875–1884.

304. Li N, Li Q, Tian XQ, Qian HY, Yang YJ. Mipomersen is a promising therapy in the management of hypercholesterolemia: a meta-analysis of randomized controlled trials. *Am J Cardiovasc Drugs*. 2014;14:367–376.

305. Rader DJ, Kastelein JJ. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. *Circulation*. 2014;129:1022–1032.

306. LaRosa JC, Pedersen TR, Somaratne R, Wasserman SM. Safety and effect of very low levels of low-density lipoprotein cholesterol on cardiovascular events. *Am J Cardiol*. 2013;111:1221–1229.

307. Kostis WJ. How low an LDL-C should we go with statin therapy? *Curr Atheroscler Rep*. 2014;16:388.

308. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. *Pharmacoeconomics*. 2004;22(Suppl 3):13–23.

309. Bays HE, Jones PH, Brown WV, Jacobson TA. National Lipid Association annual summary of clinical lipidology 2015. *J Clin Lipidol*. 2014;8(6 Suppl):S1–S36.

310. Kjems L, Filozof C, Wright M, Keefe D. Association between fasting triglycerides and presence of fasting chylomicrons in patients with severe hypertriglyceridemia. *J Clin Lipidol*. 2014;8:312 (Abstract 121).

311. Viljoen A, Wierzbicki AS. Diagnosis and treatment of severe hypertriglyceridemia. *Expert Rev Cardiovasc Ther*. 2012;10:505–514.

312. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2960–2984.

313. Yokoyama M, Origasa H, Matsuzaki M, et al, Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090–1098 Erratum in Lancet. 2007;370:220.

314. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574 Erratum in N Engl J Med. 2010;362:1748.

315. Guyton JR, Slee AE, Anderson T, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 2013;62:1580–1584.

316. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardioavscular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. 2011;217:492–498.

317. Rojas-Fernandez CH, Goldstein LB, Levey AI, Taylor BA, Bittner V. An assessment by the Statin Cognitive Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S5–S16.

318. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S58–S71.

319. Ito MK, Maki KC, Brinton EA, Cohen JD, Jacobson TA. Muscle symptoms in statin users, associations with cytochrome P450, and membrane transporter inhibitor use: a subanalysis of the USAGE study. *J Clin Lipidol*. 2014;8:69–76.

320. Kellick KA, Bottorff M, Toth PP. A clinician's guide to statin drug-drug interactions. *J Clin Lipidol*. 2014;8(3 Suppl):S30–S46.

321. Gudzune KA, Monroe AK, Sharma R, Ranasinghe PD, Chelladurai Y, Robinson KA. Effectiveness of combination therapy with statin and another lipid-modifying agent compared with intensified statin monotherapy. A systematic review. *Ann Intern Med*. 2014;160:468–476.

322. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–7422.

323. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy; a meta-analysis. *JAMA*. 2011;305:2556–2564.

324. Maki KC, Ridker PM, Brown WV, Grundy SM, Sattar N. An assessment by the Statin Diabetes Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S17–S29.

325. Waters DD, Ho JE, Boekholdt SM, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. *J Am Coll Cardiol*. 2013;61:148–152.

326. Sasaki J, Yokoyama M, Matsuzaki M, et al, JELIS Investigators. Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). *J Atheroscler Thromb*. 2012;19:194–204.

327. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010;363:692–694.

328. Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the Ezetimibe Add-on to Statin for Effectiveness (EASE) trial. *Mayo Clin Proc*. 2005;80:587–595.

329. Katsiki N, Theocharidou E, Karagiannis A, Athyros VG, Mikhailidis DP. Ezetimibe therapy for dyslipidemia: an update. *Curr Pharm Des*. 2013;19:3107–3114.

330. Laufs U, Weintraub WS, Packard CJ. Beyond statins: what to expect from add-on lipid regulating therapy? *Eur Heart J*. 2013;34:2660–2665.

331. Johns DG, Duffy J, Fisher T, Hubbard BK, Forrest MJ. On- and off-target pharmacology of torcetrapid: current understanding and implications for the structure activity relationships (SAR), discovery and development of cholesteryl ester-transfer protein (CETP) inhibitors. *Drugs*. 2012;72:491–507.

332. Lim S, Sakuma I, Quon MJ, Koh KK. Potentially important considerations in choosing specific statin treatments to reduce overall morbidity and mortality. *Int J Cardiol*. 2013;167:1696–1702.

333. Robinson JG, Colhoun HM, Bays HE, et al. Efficacy and safety of aliocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. *Clin Cardiol*. 2014;37:597–604.

334. Verma DR, Brinton EA. Management of hypercholesterolemia for prevention of atherosclerotic cardiovascular disease: focus on the potential role of recombinant anti-PCSK9 monoclonal antibodies. *Rev Cardiovasc Med*. 2014;15:86–101.

335. Toth PP. Emerging LDL therapies: mipomersen-antisense oligonucleotide therapy in the management of hypercholesterolemia. *J Clin Lipidol*. 2013;7(3 Suppl):S6–S10.

336. Goldberg AC. Emerging low-density lipoprotein therapies: microsomal triglyceride transfer protein inhibitors. *J Clin Lipidol*. 2013;7(3 Suppl):S16–S20.

337. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on familial hypercholesterolemia. *J Clin Lipidol*. 2011;5:133–140.

338. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compare with moderate lipid-lowering statin therapy after acute coronary syndromes form the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22) Trial. *J Am Coll Cardiol*. 2009;54:2358–2362.

339. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med*. 2011;365:2078–2087.

340. Puri R, Nissen SE, Shao M, et al. Antiatherosclerotic effects of long-term maximally intensive statin therapy after acute coronary syndrome: insights from study of coronary atheroma by intravascular ultrasound: effect of rosuvastatin versus atorvastatin. *Arterioscler Thromb Vasc Biol*. 2014;34:2465–2472.

341. van de Woestijne AP, Wassink AM, Monajemi H, et al, SMART study group. Plasma triglyceride levels increase the risk for recurrent vascular events independent of LDL-cholesterol or non-HDL-cholesterol. *Int J Cardiol*. 2013;167:403–408.

342. Ezhov MV, Safarova MS, Afanasieva OI, Kukharchuk VV, Pokrovsky SN. Lipoprotein(a) level and apolipoprotein(a) phenotype as predictors of long-term cardiovascular outcomes after coronary artery bypass grafting. *Atherosclerosis*. 2014;235:477–482.