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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Review of Clinical Practice Guidelines for the Management of LDL-Related Risk

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ABSTRACT

Managing risk related to low-density lipoprotein (LDL) is vital in therapy for patients at risk for atherosclerotic cardiovascular disease (ASCVD) events given its important etiologic role in atherogenesis. Despite decades of research showing reduction of ASCVD risk with multiple approaches to lowering of LDL cholesterol, there continue to be significant gaps in care with inadequate numbers of patients receiving standard of care lipid-lowering therapy. Confusion regarding implementation of the multiple published clinical practice guidelines has been identified as one contributor to suboptimal management of LDL-related risk. This review summarizes the current guidelines for reduction of LDL-related cardiovascular risk provided by a number of major professional societies, which have broad applicability to diverse populations worldwide. Statements have varied in the process and methodology of development of recommendations, the grading system for level and strength of evidence, the inclusion or exclusion of expert opinion, the suggested ASCVD risk assessment tool, the lipoproteins recommended for risk assessment, and the lipoprotein targets of therapy. The similarities and differences among important guidelines in the United States and internationally are discussed, with recommendations for future strategies to improve consistency in approaches to LDL-related ASCVD risk and to reduce gaps in implementation of evidence-based therapies. (J Am Coll Cardiol 2014;64:196–206) © 2014 by the American College of Cardiology Foundation.

Low-density lipoprotein (LDL) plays a significant role in the promotion, development, and progression of vascular atherosclerosis through a pathway that involves endothelial cell dysfunction, lipid oxidation and accumulation, foam cell formation, and inflammatory responses (1). Decades of clinical research have conclusively demonstrated that lowering of low-density lipoprotein cholesterol (LDL-C), whether by a low-saturated fat diet, partial ileal bypass surgery, or cholesterol-lowering medications, can significantly improve atherosclerotic cardiovascular disease (ASCVD) risk factors and reduce the risk of ASCVD events, including myocardial infarction, stroke, and coronary heart disease (CHD) death (2–4). Despite published clinical practice recommendations for the management

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of LDL-related cardiovascular risk, there are inadequate numbers of appropriate patients receiving standard of care lipid-lowering therapy (5,6). Numerous factors may contribute to gaps in care and confusion regarding implementation of appropriate guidelines for various patient populations may play a contributory role in suboptimal patient management.

In March 2013, the American College of Cardiology (ACC) Executive Committee approved a 3-year, multistakeholder quality initiative program, LDL: Address the Risk, to improve patient outcomes by increasing awareness of gaps in lipid management and the importance of managing LDL-related risk. One component of this program, the LDL: Address the Risk Think Tank, was convened on October 10, 2013, at the ACC's Heart House in Washington, DC. Participants in this conference included representatives of 17 medical specialty societies and other experts in cardiovascular disease risk reduction and lipidology. The purpose of this review is to summarize concerns regarding gaps in care related to implementation of the plethora and sometimes discordant clinical practice guidelines for the management of LDL-related risk, which were highlighted during the LDL: Address the Risk Think Tank. The discussion evaluates guidelines with broad applicability in large populations worldwide. We also highlight similarities and differences in the process and methodology for formulation of recommendations, the inclusion/exclusion of expert opinion and evidence from large randomized controlled trials (RCTs) and meta-analyses, the methodology for grading the strength and level of evidence, the recommended algorithms used for cardiovascular risk assessment, specific lipoprotein targets of therapy, and consideration of special patient populations.

GUIDELINES FOR THE MANAGEMENT OF LDL-RELATED ASCVD RISK

NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL. In 2001 and 2002, the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) published updated recommendations for cholesterol testing and management (7,8) (**Central Illustration**). Each evidence statement was presented with the category or type of supporting evidence and the strength of the evidence. The standard fasting lipid panel was considered the preferred initial test. ATP III focused on intensive treatment of patients with manifest CHD, but also recognized the significant CHD risk present in persons with multiple risk factors. The Framingham risk assessment algorithm for projection of *10-year absolute CHD risk* was recommended to identify patients with multiple risk factors who would benefit from more intensive therapy (9) (**Table 1**). Diabetes was reclassified as a CHD "risk equivalent," and patients with multiple metabolic risk factors (metabolic syndrome) were identified as candidates for intensified therapeutic lifestyle changes. In the ATP III guidelines, optimal LDL-C was identified as <100 mg/dl and low high-density lipoprotein cholesterol (HDL-C) was raised from <35 to <40 mg/dl. In patients with triglyceride levels ≥200 mg/dl, the calculation of non-HDL-C (total cholesterol − HDL-C) was recommended for consideration of treatment beyond LDL lowering. Thus, LDL-C was considered the primary target of therapy and non-HDL-C as a secondary treatment goal in patients with hypertriglyceridemia. The 2004 update of ATP III (10) considered 5 major recent clinical outcome trials published between 2001 and 2004, which addressed issues not previously considered in clinical trials of cholesterol lowering (11–15). These trials supported the consideration of diabetes as a high-risk category/CHD risk equivalent, the benefit of LDL-C lowering in older persons, an optional goal of LDL-C ≤70 mg/dl in very high-risk patients, and combination therapy with statin plus a fibrate or niacin in patients with triglycerides ≥200 mg/dl or low HDL-C. The NCEP ATP III guidelines and 2004 update have served as the standard of care for at-risk patients with hyperlipidemia for nearly a decade in the United States.

INTERNATIONAL ATHEROSCLEROSIS SOCIETY. The International Atherosclerosis Society (IAS) Position Paper on Global Recommendations for the Management of Dyslipidemia was published online in July 2013, and recommendations were based on international consensus among experts from multiple regions around the world (16). Given the strength of evidence in secondary ASCVD prevention, priority was given to RCTs to inform and guide recommendations in this high-risk population. For primary prevention, a limited number of RCTs and few multinational studies were considered. Thus, the recommendations for patients without manifest ASCVD were based on epidemiologic, genetic, and basic research, as well as available clinical trials. A discussion of the IAS expert panel deliberations are reviewed for each recommendation, which provides insight into

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

Apo = apolipoprotein

ASCVD = atherosclerotic cardiovascular disease

CHD = coronary heart disease

CVD = cardiovascular disease

FRS = Framingham Risk Score

HDL-C = high-density lipoprotein cholesterol

IAS = International Atherosclerosis Society

LDL = low-density lipoproteins

LDL-C = low-density lipoprotein cholesterol

NHLBI = National Heart, Lung, and Blood Institute

RCT = randomized controlled trial

SOURCE	Recommended Lipoprotein Measurements for Risk Assessment	Recommended Lipoprotein Targets of Therapy	Recommended Risk Assessment Algorithm
National Cholesterol Education Program Adult Treatment Panel III[7,8]	Fasting lipid panel Calculation of non-HDL-C when TG >200 mg/dl	Primary target: LDL-C Secondary target: non-HDL-C	Identify number of CHD risk factors Framingham 10-year absolute CHD risk
International Atherosclerosis Society[16]	Fasting lipid panel with calculation of non-HDL-C	Non-HDL-C LDL-C is considered alternative target of therapy	Lifetime risk of total ASCVD morbidity/mortality (by Framingham, CV Lifetime Risk Pooling Project, or QRISK)
European Society of Cardiology/European Atherosclerosis Society[22]	Fasting lipid panel with calculation of non-HDL-C and TC/HDL-C ratio apoB or apoB/apoA1 ratio are considered alternative risk markers	Primary target: LDL-C Secondary targets: non-HDL-C or apoB in patients with cardiometabolic risk	10-year total fatal ASCVD risk by the Systematic Coronary Risk Evaluation (SCORE) system
Canadian Cardiovascular Society[27]	Fasting lipid panel with calculation of non-HDL-C apoB considered alternative marker of risk	Primary target: LDL-C Secondary targets: non-HDL-C and apoB	10-year risk of total ASCVD events by the Framingham Risk Score
American Association of Clinical Endocrinologists[31]	Fasting lipid panel Calculation of non-HDL-C more accurate risk assessment if TG in between 200–500 mg/dl, diabetes, insulin resistance, or established CAD	Primary target: LDL-C Secondary targets: non-HDL- in patients with cardiometabolic risk or established CAD apoB recommended to assess success of LDL-C-lowering therapy	Men: Framingham Risk Score 10-year risk of coronary event Women: Reynolds Risk Score (10-year risk of coronary event, stroke, or other major heart disease)
American Diabetes Association/ American Heart Association Statement on Cardiometabolic Risk[38]	Stronger risk discrimination provided by non-HDL-C, apoB, LDL-P	Strong recommendation for apoB and non-HDL-C as secondary targets	30-year/lifetime global ASCVD risk
American Diabetes Association: Standards of Medical Care in Diabetes[39]	Fasting lipid panel	LDL-C	Not applicable in setting of diabetes (CHD risk equivalent)
Kidney Disease: Improving Global Outcomes: Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease[41]	Fasting lipid panel to screen for more severe forms of dyslipidemia and secondary causes of dyslipidemia	None: therapy guided by absolute risk of coronary event based on age, Stage of CKD or eGFR	CKD considered CHD risk equivalent Treatment with evidence-based statins/statin doses based on age, Stage of CKD or eGFR
Secondary Prevention of Atherosclerotic Cardiovascular Disease in Older Adults: A Scientific Statement from the American Heart Association[36]	Fasting lipid panel Calculation of non-HDL-C when TG >200 mg/dl	Primary target: LDL-C Secondary target: non-HDL-C	N/A
National Lipid Association: Familial Hypercholesterolemia[40]	Fasting lipid panel	LDL-C	Not applicable due to extremely high lifetime risk
Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[34,35]	Fasting lipid panel with calculation of non-HDL-C	Primary target: LDL-C Secondary target: non-HDL-C	No risk algorithm, treatment based on number of ASCVD risk factors
AHA Women's Cardiovascular Disease Prevention Guidelines[37]	Fasting lipid panel Consider hs-CRP in women >60 years and CHD risk >10%	LDL-C	Updated Framingham risk profile (coronary, cerebrovascular, and peripheral arterial disease and heart failure events) Reynolds Risk Score (10-year risk of coronary event, stroke, or other major heart disease)
2013 American College of Cardiology/American Heart Association: Blood Cholesterol Guidelines for ASCVD Prevention[50]	Fasting lipid panel to screen for more severe forms of dyslipidemia and secondary causes of dyslipidemia	LDL-C measured for assessment of therapeutic response and compliance Therapy guided by identification of 4 categories of patients who benefit from high or moderate-dose statin therapy	CV Risk Calculator based on Pooled Risk Equations (10-year risk of total ASCVD events) Lifetime risk provided for individuals 20–59 years of age

CENTRAL ILLUSTRATION **Comparison of Clinical Guidelines for the Management of Risks Related to LDL in ASCVD**

apoA1 = apolipoprotein A1; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; TC = total cholesterol; TG = triglycerides.

considerations of the type and strength of available evidence evaluated. The goal of the IAS document is to integrate existing guidelines and provide international consensus guidelines with worldwide applicability. The guideline assigns priority to assessment of *lifetime risk of total ASCVD morbidity and/or mortality*, rather than 10-year risk, as the authors considered this to be the purpose of primary prevention. Four long-term risk assessment tools are reviewed for primary prevention (2 from Framingham, the Cardiovascular Lifetime Risk Pooling Project, and QRISK [17–21]), and recommendations are made for appropriate selection or recalibration of risk algorithms for specific ethnic populations. The IAS favors non-HDL-C as the major target of lipid-lowering therapy, as these experts consider it to be more reflective of atherogenicity in the presence of elevated triglycerides. Also, non-HDL-C can be measured in the nonfasting state. LDL-C is considered an alternate target of treatment. The IAS defines "optimal levels" of atherogenic lipoproteins in primary and secondary prevention, which are identical to those of ATP III, but *does not* provide specific treatment goals. Finally, the society recommends that the intensity of therapy be adjusted to the patient's long-term ASCVD risk, and the potency of therapy be based on the provider's clinical judgment.

EUROPEAN SOCIETY OF CARDIOLOGY/EUROPEAN ATHEROSCLEROSIS SOCIETY. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias, published in 2011, present comprehensive recommendations for lipid-lowering therapy in primary and secondary prevention in the general European population, as well as special and regional populations (22). Following a systematic review of the literature, each proposed recommendation includes a description of the class of evidence and the level of evidence. Similar to NCEP ATP III and IAS, the ESC/EAS guidelines recommend that the intensity of lipid therapy be adjusted to the level of risk. However, estimation of *10-year total fatal ASCVD risk* (first fatal atherosclerotic event, heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death) by the SCORE (Systematic Coronary Risk Estimation) system is recommended as the preferred risk assessment algorithm (23). Low- and high-risk charts are provided for adjustment of risk assessments in specific countries in Europe. The initial patient evaluation should include a full lipid panel, as well as a non-HDL-C and triglyceride/HDL-C ratio. Apolipoprotein B (Apo B) or Apo B/Apo A1 may be considered as alternate risk markers. LDL-C is recommended as the primary target of therapy. In agreement with the NCEP ATP III update, for patients at very high risk (established ASCVD, diabetes, chronic kidney disease (CKD), or 10-year total ASCVD risk of ≥10% by SCORE), the target LDL-C level is <70 mg/dl or ≥50% reduction when target level cannot be reached. For patients at high ASCVD risk (markedly elevated single ASCVD risk factor or SCORE ≥5 to <10%) an LDL-C goal of <100 mg/dl is suggested. In patients with the metabolic syndrome, diabetes, or CKD with combined dyslipidemias, the ESC/EAS guidelines suggest that non-HDL-C or Apo B may be measured and considered as a secondary target of therapy, similar to recommendations of the NCEP ATP III update for assessment of non-HDL-C. More recent publications including the updated European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012) (24), the 2013 ESC Guidelines on the Management of Stable Coronary Artery Disease (25), and the ESC Guidelines on Diabetes, Pre-Diabetes, and Cardiovascular Diseases in collaboration with the European Association for the Study of Diabetes (26) all have subsequently supported these earlier recommendations of the ESC/EAS Dyslipidaemia Management Guidelines.

CANADIAN CARDIOVASCULAR SOCIETY. The Canadian Cardiovascular Society (CCS) updated its Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult in 2012 (27). The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (28) was used as the standard for consideration of scientific evidence (strength and quality of evidence). In agreement with the NCEP ATP III, IAS, and ESC/EAS guidelines, the CCS suggests that the intensity of treatment be modulated by the level of ASCVD risk. The recommended risk assessment algorithm is the Framingham Risk Score (FRS) to estimate the *10-year risk of total ASCVD events* (29). If a family history of premature ASCVD among first-degree relatives is present, the FRS risk estimate is doubled and is referred to as the *modified FRS*. LDL-C remains the primary treatment target, with an optimal LDL-C level of ≤2.0 mmol/l or approximately 77 mg/dl. Non-HDL-C and Apo B are considered to have a strong recommendation and high-quality evidence as alternative treatment targets for optimal risk reduction (non-HDL-C ≤2.6 mmol/l, Apo B ≤80 mg/dl). Secondary testing is considered of possible benefit in intermediate-risk patients with FRS 5% to 19% and may include lipoprotein(a), high-sensitivity C-reactive protein (hs-CRP), coronary calcium scoring, ankle brachial index, or other noninvasive measurements.

TABLE 1 Comparison of ASCVD Risk Assessment Tools

Source	Recommended Risk Assessment Tool	Forecast Capability of Tool (yrs)	Risk Factors Included for Risk Estimation	Atherosclerotic Cardiovascular Disease Outcome Predicted	Population Used for Derivation/Validation of Risk Algorithm
National Cholesterol Education Program Adult Treatment Panel III (7,8)	Original Framingham Risk Score (9)	10	Sex, age, TC, HDL-C, blood pressure, diabetes, smoking status	Myocardial infarction and coronary heart disease death	• Framingham original and offspring cohorts • Men, n = 2,489 • Women, n = 2,856 • Ages 30–74 yrs • Caucasian
International Atherosclerosis Society (16)	Updated Framingham Risk Score (17) with recalibration coefficients for different patient populations	Lifetime	Risk factor status age 50 yrs: TC, systolic blood pressure, diastolic blood pressure, smoking status, diabetes	Myocardial infarction, coronary insufficiency, angina, stroke, claudication, CVD death based on measured risk factors at age 50 yrs	• Framingham original and offspring cohorts • Men, n = 3,564 • Women, n = 4,362 • Ages 30–74 yrs • Caucasian
European Society of Cardiology/European Atherosclerosis Society (22)	SCORE (23) Systematic Coronary Risk Evaluation (with risk adjustment algorithm/tables provided based on population/country)	10	TC or TC/HDL-C ratio, sex, smoking status, systolic blood pressure	Fatal atherosclerotic event (myocardial infarction, stroke, occlusive arterial disease, sudden cardiac death)	• 104,961 subjects from 7 pooled European (Belgium, Britain, Denmark, Finland, Germany, Italy, Spain) prospective studies • Men, 55% (ages 20–89 yrs) • Women, 45% (ages 20–99 yrs)
Canadian Cardiovascular Society (27)	Framingham Risk Score: Global Cardiovascular Disease Risk (29) Modified Framingham Risk Score (multiply score by 2 in presence of family history of premature ASCVD) (27)	10	Age, sex, TC, HDL-C, systolic blood pressure, blood pressure treatment, smoking status, diabetes, vascular age	Absolute ASCVD event (coronary heart, cerebrovascular, peripheral vascular, and heart failure)	• Framingham original and offspring cohorts • Men, n = 3,969 • Women, n = 4,522 • Ages 30–74 yrs • Caucasian
American Association of Clinical Endocrinologists (30)	Men: Original Framingham Risk Score (9) Adult Treatment Panel III	10	Sex, age, TC, HDL-C, blood pressure, diabetes, smoking status	Framingham Risk Score: Myocardial infarction and coronary heart disease death	Framingham original and offspring cohorts • Men, n = 2,489 • Women, n = 2,856 • Ages 30-74 yrs • Caucasian
	Women: Reynolds Risk Score (32,33)	10	Age, systolic blood pressure, HgbA1C if diabetic, current smoking, TC, HDL-C, hs-CRP, family history premature ASCVD	Reynolds Risk Score: Myocardial infarction, ischemic stroke, coronary revascularization, and cardiovascular death	• Women's Health Study • Women, n = 24,558 • Ages 48–59 yrs • Caucasian = 95% • Black = 1.9% • Asian = 1.4%
Kidney Disease: Improving Global Outcomes: Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease (41)	Kidney Disease: Improving Global Outcomes Coronary Risk Assessment (45)	10	Age, estimated glomerular filtration rate	Myocardial infarction or coronary heart death by age and estimated glomerular filtration rate	• Alberta Kidney Disease Network • N = 1,268,029 • Women, 50% • Mean age = 49.4 yrs

Continued on the next page

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS. The 2012 update of the American Association of Clinical Endocrinologists' (AACE) Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis (30) were developed according to the AACE Protocol for Standardized Production of Clinical Practice Guidelines-2010 update (31). Each recommendation is assigned an evidence level based on the quality of evidence, and the evidence is also rated for strength. The FRS (9) and Reynolds Risk Score (32,33) are the recommended risk assessment tools in the AACE guidelines. The latter is preferred for CAD risk assessment in women, as the FRS can underestimate 10-year risk in women with 2 risk factors. A fasting lipid profile is the recommended baseline evaluation for cardiovascular risk detection. In the presence of elevated triglycerides (200 to 500 mg/dl), diabetes, insulin resistance, and/or established CAD calculation of non-HDL-C is considered to provide more accurate risk assessment than LDL-C alone. The AACE guidelines also recommend measurement of Apo B to assess the success of LDL-C-lowering therapy as Apo B reflects LDL particle number, which may be elevated in patients at

TABLE 1 Continued

Source	Recommended Risk Assessment Tool	Forecast Capability of Tool (yrs)	Risk Factors Included for Risk Estimation	Atherosclerotic Cardiovascular Disease Outcome Predicted	Population Used for Derivation/Validation of Risk Algorithm
Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update (37)	Framingham Risk Score: Global Cardiovascular Disease Risk (19)	10	Age, sex, TC, HDL-C, systolic blood pressure, blood pressure treatment, smoking status, diabetes	Framingham Risk Score: Absolute ASCVD event (coronary heart, cerebrovascular, peripheral vascular, and heart failure)	Framingham original and offspring cohorts • Men, n = 3,969 • Women, n = 4,522 • Ages 30–74 yrs • Caucasian
	Reynolds Risk Score (32,33)	10	Age, sex, systolic blood pressure, HgbA1C if diabetic, current smoking, TC, HDL-C, hs-CRP, family history premature ASCVD	Reynolds Risk Score: Myocardial infarction, ischemic stroke, coronary revascularization, and cardiovascular death	• Women's Health Study • Women, n = 24,558 • Ages 48–59 yrs • Caucasian = 95% • Black = 1.9% • Asian = 1.4%
2013 American College of Cardiology/American Heart Association Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (50)	Cardiovascular Risk Calculator based on Pooled Cohort Risk Equations (52)	10 Lifetime or 30 (for ages 20–59 yrs)	Age, sex, ethnicity (Caucasian or African American), TC, HDL-C, systolic blood pressure, treatment for hypertension, diabetes	Nonfatal myocardial infarction, coronary heart disease death, fatal or nonfatal stroke	• Atherosclerosis Risk in Communities • Cardiovascular Health Study • Coronary Artery Risk Development in Young Adults • Framingham Original and Offspring Studies • African American, white men and women • Ages 40–74 yrs

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HgbA1C = hemoglobin A1C; hs-CRP = high-sensitivity C-reactive protein; TC = total cholesterol.

or below LDL-C goal. Recommended treatment goals are similar to ATP III with the addition of optimal Apo B levels <90 mg/dl in primary prevention and <80 mg/dl in patients with established CAD or diabetes.

MANAGEMENT OF LDL-RELATED ASCVD RISK IN SPECIAL POPULATIONS

Adding to the confusion for practitioners selecting appropriate recommendations for the management of LDL-related risk in individual patients is the multitude of published guidelines for special populations: children, the elderly, women, and patients with cardiometabolic risk or diabetes, CKD, and familial hypercholesterolemia, among others (34-40). The unique features of these guidelines are summarized in the **Central Illustration**. It is of interest to specifically review the newest recommendations for management of LDL-related risk in patients with CKD, which represent a change in the approach to lipoprotein targets of therapy.

CHRONIC KIDNEY DISEASE. The 2013 Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease (41), published by the Kidney Disease: Improving Global Outcomes (KDIGO) panel, represents a significant departure from the previous guidelines of the Kidney Disease Outcomes Quality Initiative group in 2003 (42) and 2007 (43). The international group of experts in nephrology, cardiology, epidemiology, and lipidology used the GRADE system for evaluation of the evidence. However, the group acknowledges that the recommendations are primarily supported by a few large RCTs and post hoc analyses of the subgroup of CKD patients from statin trials in the general population. In patients with CKD, an initial fasting lipid profile is recommended primarily for the purpose of identification of more severe forms of hypercholesterolemia or hypertriglyceridemia and to rule out remediable or secondary causes of dyslipidemia. However, evidence from the Alberta Kidney Disease Network has demonstrated that in patients with CKD who are not dependent on dialysis, the relationship between LDL-C and ASCVD events is weaker than in the general population (44,45). This may possibly be related to the atherogenic dyslipidemia often present in CKD, which is characterized by lower levels of LDL-C, elevated LDL particle concentration, an increase in small dense LDL, reduced HDL-C, and elevated triglycerides (44). Therefore, according to KDIGO guidelines, the measured LDL-C may be less useful as a marker of coronary risk among people with advanced CKD who are not dialysis dependent, and it does not serve as an indication for pharmacological treatment. Instead, therapy is guided by the *absolute risk of coronary events* based on patient age and stage of CKD or estimated glomerular filtration rate (eGFR) (45) (**Table 2**). The rate of coronary death or incident MI among CKD patients age >50 years (both

TABLE 2 Rate of Coronary Death or Nonfatal MI (by Age and eGFR)

	Rate (95% CI) of Coronary Death or Nonfatal MI (per 1,000 Patient-Years)		
	Overall	Male	Female
Age >40 yrs (eGFR G1-G4)	14.9 (14.6-15.3)	17.4 (16.9-17.9)	12.7 (12.3-13.1)
eGFR G3a-G4	19.3 (18.8-19.8)	23.4 (22.6-24.2)	16.4 (15.8-17.0)
eGFR G1-G2	9.7 (9.3-10.0)	12.0 (11.4-12.6)	6.7 (6.3, 7.2)
Age >50 yrs (eGFR G1-G4)	17.3 (17.0-17.7)	20.2 (19.6-20.8)	14.8 (14.3-15.3)
eGFR G3a-G4	19.9 (19.4-20.4)	24.3 (23.4-25.2)	16.9 (16.3-17.5)
eGFR G1-G2	12.9 (12.4-13.4)	15.2 (14.5-16.0)	9.7 (9.0-10.5)
Age 40-50 yrs (eGFR G1-G4)	3.2 (2.9-3.6)	4.7 (4.2-5.4)	1.6 (1.2-2.0)
eGFR G3a-G4	4.7 (3.7-6.0)	5.9 (4.3-8.1)	3.6 (2.5-53)
eGFR G1-G2	3.0 (2.6-3.3)	4.6 (4.0-5.3)	1.2 (0.9-1.6)

Values are unadjusted rates from 1,268,029 participants in the Alberta Kidney Disease cohort. People with diabetes, MI, and other cardiovascular disease were included. Data do not apply to people with Kidney transplants. Reproduced with permission from KDIGO (41).

CI = confidence interval; eGFR = estimated glomerular filtration; MI = myocardial infarction.

men and women) is consistently >10 per 1,000 patient-years, which is considered by these experts to indicate a potential benefit of statin therapy. Specific doses of individual statins are recommended for each stage of CKD or eGFR, and dose titration is not indicated according to the evidence reviewed. Statin therapy or combination therapy with statin and ezetimibe is not recommended in adults with dialysis-dependent CKD due to lack of evidence of ASCVD risk reduction in patients with stage V CKD (46-48). Epidemiologic evidence suggests that cardiovascular events in dialysis patients tend to be nonatherosclerotic and more likely related to heart failure and arrhythmias (49). However, therapy may be continued in patients already receiving therapy at the time of initiation of dialysis. The KDIGO guidelines suggest follow-up measurement of lipid levels only when the results would influence therapy: that is, monitoring of adherence to statin therapy or to assess 10-year cardiovascular disease (CVD) risk in younger CKD patients not currently on statin therapy. Further discussion of this approach will follow in the review of the newest guidelines from the ACC/American Heart Association (AHA) on the management of blood cholesterol (50).

MANAGEMENT OF LDL-RELATED CVD RISK: A CHANGE IN STRATEGY

In the United States, the methodology for development of guidelines and the fundamental approach to management of LDL-related CVD risk changed significantly with the publication of the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the ACC/AHA Task Force on Practice Guidelines in November 2013 (50). The guideline formulation process began in 2008 when an Expert Panel of the National Heart, Lung, and Blood Institute (NHLBI) initiated a systematic review of the evidence and development of critical questions concerning management of dyslipidemias and ASCVD risk reduction as a foundation for publication of new ATP IV guidelines. Therefore, unlike ATP III, the new guidelines address only a limited number of critical questions and do not provide comprehensive recommendations for the management of many forms of dyslipidemia. The NHLBI subsequently initiated collaboration with the ACC, AHA, and other supporting organizations for the process of guideline formulation, and the final document now serves as the most current U.S. guidelines for management of blood cholesterol for CVD risk reduction (51).

In the 2013 ACC/AHA blood cholesterol guidelines, the inherent differences between the evidence grading systems of the NHLBI and the ACC/AHA required mapping of recommendations to each format. The NHLBI grading format includes the strength of the recommendation and a quality rating of the strength of the evidence. The ACC/AHA Class of Recommendation/Level of Evidence construct includes the size of the treatment effect and an estimate of the precision or certainty of the treatment effect. As stated in the new guidelines, for some recommendations the alignment between the 2 grading systems is not perfect, and explanations of the variations are discussed when present.

For primary prevention of ASCVD, the recommended risk assessment tool in the ACC/AHA guidelines is the new CV Risk Calculator based on the pooled cohort equations, as described in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (52). The equations are derived from large, diverse, community-based cohorts that are generally representative of the U.S. population of whites and African Americans (53-57). The calculator provides race- and sex-specific estimates of the *10-year risk of first hard ASCVD event* (nonfatal myocardial infarction, CHD death, fatal, or nonfatal stroke) and should be used in non-Hispanic African Americans and non-Hispanic whites between 40 and 79 years of age. *Lifetime- or 30-year risk* also is provided for individuals age 20 to 59 years who are not at high short-term risk. Recommended optional variables and/or screening tests that may be considered to refine risk assessment include: family history of premature ASCVD; hs-CRP >2 mg/l; coronary artery calcium score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity; and ankle brachial index. Based on expert opinion, the presence of any of these screening abnormalities supports revising the patient's risk assessment to a higher level of risk.

In addition to a new risk calculator for CVD risk assessment, the ACC/AHA guidelines also recommend a novel strategy for management of LDL-related risk. As discussed in the previous text, guidelines from multiple organizations have previously focused on the fasting lipid panel as the initial evaluation of lipid-related CVD risk. Within each category of ASCVD risk, targets of treatment are then specified in these recommendations. Upon systematic review of the evidence, authors of the new ACC/AHA guidelines determined that current clinical trial data do not support this approach. Also, the data are inadequate to indicate specific lipoprotein goals of therapy. Therefore, the panel made no recommendation for or against specific targets (LDL-C or non-HDL-C) for primary or secondary ASCVD prevention. Instead, these experts identified 4 groups of patients in which there is the most extensive evidence of the benefit of statin therapy for prevention of ASCVD:

1. Individuals with clinical ASCVD;
2. Individuals with primary elevations of LDL-C ≥190 mg/dl;
3. Individuals 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dl; and
4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70 to 189 mg/dl and an estimated 10-year ASCVD risk of ≥7.5% by the Pooled Risk Equations.

For each risk group, the guidelines recommend an intensity of statin therapy, either moderate- or high-intensity. Low-intensity statins are recommended only in patients who have experienced or are at risk for adverse effects of treatment. The guidelines do not support dose titration to achieve optimal levels of LDL-C, non-HDL-C, or Apo B, as recommended in previous guidelines. Also, in a significant departure from previous guidelines, the 2013 ACC/AHA guidelines recommend measurement of on-therapy LDL-C only as an assessment of adherence and response to therapy.

GUIDELINE CONTROVERSIES AND CONFUSIONS

It is no surprise that a revolutionary change from decades of emphasis on LDL-C goals of therapy in dyslipidemia would generate considerable controversy and confusion among healthcare providers, the media, and patients. It is important to note that although there are significant changes in the new 2013 ACC/AHA guidelines, there are recommendations that are consistent with those of the NCEP ATP III, ATP III update panels, and other organizations. LDL remains the lipoprotein of interest as recommended in the previous guidelines of the ATP III and current recommendations of the IAS, EAS/ESC, CCS, AACE, KDIGO, the American Diabetes Association, the National Lipid Association, and the American Association of Pediatrics. Very high-risk patients with manifest ASCVD or familial hypercholesterolemia and/or LDL-C ≥190 mg/dl continue to be candidates for high-intensity statin therapy. Also, in patients with familial hypercholesterolemia, combination therapy with high-intensity statins and cholesterol absorption inhibitors, bile acid sequestrants, LDL apheresis, or newer therapies may be considered for additional reduction of LDL-C levels even in the absence of a specific LDL-C target. As in previous guidelines, the new ACC/AHA recommendations consider diabetic patients as a high-risk group; however, the intensity of therapy is now based on the *10-year estimate of risk of hard ASCVD event* by the pooled risk equations. Although a newly-validated risk assessment algorithm is recommended by the ACC/AHA in primary prevention patients and diabetics without ASCVD, the intensity of statin therapy is still closely related to the intensity of risk as recommended by other guidelines. The role of assessment of other biomarkers and noninvasive imaging for subclinical atherosclerosis is addressed in many of the guidelines, including the 2013 ACC/AHA, AACE, the AHA prevention guidelines in women, IAS, CCS, and EAS/ESC. The tests with the greatest incremental risk prediction and the strongest recommendations for additional testing beyond the standard algorithm include hs-CRP, coronary calcium scoring, and ankle brachial index (50). Finally, monitoring of LDL-C with follow-up laboratory data is recommended in the 2013 ACC/AHA guidelines as well as in other clinical practice guidelines. However, the value is to be used only as an assessment of compliance and response to treatment rather than as a target of therapy.

The controversies and confusions that have resulted with the release of the new guidelines are due to substantive differences in both the process of guideline development and the content of the new ACC/AHA clinical practice recommendations. The 2013 guidelines are narrower in scope and consider 3 critical questions in lipid management for ASCVD prevention. They provide discussion of evidence but limited recommendations for the treatment of special populations (age <40 to >75 years; those with CKD, HIV, inflammatory or rheumatolgic disorders, or patients status post solid organ transplantation; Asians, Hispanics, or other ethnic populations) and management of patients with complex dyslipidemias, suboptimal response to therapy, adverse effects on

statin therapy, or complete statin intolerance. The previous ATP III guidelines were considered to be the reference standard for diagnosis, treatment, and long-term follow-up of patients with the majority of lipid disorders. It is important for providers to understand that many of the common primary prevention dyslipidemia issues have not been studied in RCTs, so the new guidelines do not provide evidence-based recommendations for treating patients who do not fall clearly into 1 of the 4 groups identified. This is of particular importance in the management of pediatric patients with LDL-related risk. Due to ethical and practical issues in pediatric clinical research, there are few large RCTs, and recommendations must be based upon RCTs with minor limitations, overwhelmingly consistent evidence from long-term observational studies, and case control or cohort studies (35).

The new risk assessment tool recommended in the 2013 guidelines is based on newly-derived pooled risk equations, and concerns have been expressed regarding the applicability of this algorithm for the general population and other ethnic groups and the increased numbers of patients who qualify for moderate- to high-intensity statin therapy. Application of the new risk assessment tool in the National Health and Nutrition Surveys of 2005 and 2010 resulted in a substantial increase in adults eligible for statin therapy (12.8 million), particularly in older adults (58). In a European cohort, investigators determined that application of the new CV Risk Calculator would recommend that all men and 65% of women older than age 55 years would be candidates for treatment with a statin (59). In the study populations of the Multi-Ethnic Study of Atherosclerosis, the Women's Health Study, the Physicians' Health Study, and the Women's Health Initiative Observational Study, authors compared the observed and predicted event rates by the CV Risk Calculator, finding that the new algorithm overestimated observed risks by approximately 75% to 150% (60). However, in the Reasons for Geographic and Racial Differences in Stroke study, the observed and predicted 5-year ASCVD risks were similar when patients with diabetes, LDL-C <40 or >189 mg/dl, and current statin therapy were excluded and in Medicare participants (61). Certainly, validation of the CV Risk Calculator in other datasets will address these concerns and determine its applicability in persons at varying levels of ASCVD risk and in more ethnically-diverse populations. Finally, the risk calculator also provides 30-year or lifetime risk for patients who are age 20 to 59 years, but the guidelines provide limited specific information on treatment recommendations for individuals with high lifetime risk.

Probably, the most significant and controversial changes in the ACC/AHA recommendations are those concerning the abandonment of lipoprotein treatment targets and goals of therapy. Treatment is initiated as moderate- or high-intensity statin therapy, and dose titration to a specific LDL-C goal is no longer recommended. Only patients with a high risk of adverse events (i.e., the elderly, those with multiple comorbidities, polypharmacy) are recommended to initiate low-intensity statin therapy. Concerns regarding the initiation of therapy with high-dose, high-potency statin medications in ASCVD risk reduction should be considered. Overall, adherence to all doses of statin therapy in at-risk patients is poor in both primary prevention and high-risk populations (62–64). As the new AHA/ACC guidelines recommend initiation of only high- and moderate-intensity statins in high-risk patients, there is concern for even further reductions in compliance with prescribed statin or appropriate statin intensity.

A number of professional societies have published responses to the publication of these new ACC/AHA guidelines, and some have chosen not to endorse the recommendations based on the concerns and controversies noted in the previous text, including AACE (65) and the National Lipid Association (66). The EAS has stated that although there are similarities between the EAS/ESC and the new ACC/AHA guidelines, its leaders recommend no change in the approach to LDL-related risk (67). They continue to support LDL-C as the target of therapy and the SCORE risk assessment for the European populations as detailed in the EAS/ESC guidelines.

SUMMARY

This discussion clearly demonstrates that the number of published guidelines for the management of LDL-related ASCVD risk and the substantive differences in recommendations may contribute to confusion among providers and lead to suboptimal management of at-risk patients. It is recommended that professional societies work together in the future to develop guidelines that are based on unified principles of treatment for reduction of ASCVD risk, high-quality evidence from large RCTs, as well as other types of research that inform us regarding mechanisms of atherogenesis. In addition, a focus on special patient populations will remain important in the process of guideline development, as there are a number of patients excluded from specific ACC/AHA recommendations. Education of providers regarding the process of guideline development and strategies for integration of existing guidelines will be

important to successfully manage high-risk patients. Clinicians and patients will benefit from the understanding that these recommendations serve only as a starting point for care of the individual patient. Clinical judgment and patient preference must play important roles in the therapeutic decision.

In the meantime, clinicians have questions regarding the wave of change in the new recommendations and request simple tools for implementation of guidelines into daily practice. There are also numerous questions regarding management of patients not considered in 1 of the 4 statin benefit groups, patients with high lifetime ASCVD risk, and patients with complex dyslipidemias. Many patients question the implications of initiation of therapy with high-dose statins, the lack of specific numeric goals of therapy, and reduced monitoring of statin therapy by laboratory assessment. Patients require a careful explanation of the risks of dyslipidemia and a better understanding of the benefits of lifestyle therapy as well as the risks and benefits of pharmacologic strategies for management of LDL-related risk. The ACC's LDL: Address the Risk program will use the information reviewed during the Think Tank to develop more effective strategies for clinicians to assist in the implementation of evidence-based guidelines and for patients to improve compliance with proven preventive lipid-lowering therapy.

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