Recent Update to the US Cholesterol Treatment Guidelines
A Comparison With International Guidelines

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Abstract—The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline advocated several changes from the previous Adult Treatment Panel III guidelines. Assuming full implementation, the 2013 ACC/AHA guideline would identify ≈13 million Americans as newly eligible for consideration of statin therapy. Three features of the 2013 ACC/AHA guideline primarily responsible for these differences are the specific risk assessment tool endorsed, the risk threshold considered sufficient to warrant primary prevention statin therapy, and the decision not to include cholesterol treatment targets. There is no consensus among international guidelines on the optimal approach to these 3 components. The 2013 ACC/AHA guideline recommends assessing absolute risk with the Pooled Cohort equations, which were developed to improve on previous risk assessment models by including stroke as an outcome and by broadening racial and geographic diversity. Each of the leading international guidelines recommends a different equation for absolute risk assessment. The 2013 ACC/AHA guideline advises consideration of statin therapy for an estimated 10-year risk of atherosclerotic vascular disease of ≥7.5%, which is lower than the thresholds recommended by other leading international guidelines. Lastly, the 2013 ACC/AHA guideline does not endorse a treat-to-target strategy but instead specifies the appropriate intensity of statin for each risk category. This approach is shared by the National Institute for Health and Care Excellence guidelines but differs from other international guidelines. In this review, we summarize the 2013 ACC/AHA cholesterol guideline recommendations and compare them with recommendations from Adult Treatment Panel III and other leading international guidelines. **(*Circulation*. 2016;133:1795-1806. DOI: 10.1161/CIRCULATIONAHA.116.021407.)**

Key Words: cardiovascular diseases ■ cholesterol ■ guideline [publication type] ■ prevention and control

Despite reductions in the mortality rate for cardiovascular disease (CVD) among high- and middle-income countries during the past 2 decades, approximately one third of global deaths are still attributable to ischemic heart disease and stroke.[1] These conditions also account for a large proportion of disability and global healthcare costs.[2,3] Elevated blood cholesterol is among the most prevalent modifiable cardiovascular risk factors, with medical therapies proven to reduce both CVD incidence and related mortality.[4–10] Therefore, clinical practice guidelines addressing the treatment of blood cholesterol have a tremendous potential impact on population health and related healthcare costs. The most recent US guidelines on the treatment of blood cholesterol[11] contain important changes from the previous version.[12,13] In this review, we aim to summarize the recommendations from the most recent US cholesterol guideline, highlighting specific changes from the previous version, and in parallel compare it with other leading international guidelines.

Guidelines for the Treatment of Blood Cholesterol

Clinical Vignette

To demonstrate differences between the various guidelines, we refer to a representative patient (Figure): Consider a 60-year-old nonsmoking white man without established CVD or diabetes mellitus with no family history of premature CVD who currently takes no medications. He is 69 in (175 cm) tall and weighs 180 lb (81.6 kg); his body mass index is 26.6 kg/m^2; his blood pressure is 144/86 mm Hg; and his fasting lipid profile reveals a total serum cholesterol of 195 mg/dL, low-density lipoprotein (LDL) cholesterol (LDL-C) of 125 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 50 mg/dL, and triglycerides of 100 mg/dL (to convert from mg/dL to mmol/L, multiply LDL-C or HDL-C by 0.0259 and multiply triglycerides by 0.0113).

2013 American College of Cardiology/American Heart Association Guideline

Methodology

The 2013 American College of Cardiology/American Heart Association "Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults"[11] (2013 ACC/AHA guideline) was commissioned to reflect new evidence since the previous Adult Treatment Panel III (ATP III) guidelines were last updated in 2004.[12,13] Whereas previous cholesterol guidelines targeted the prevention of coronary

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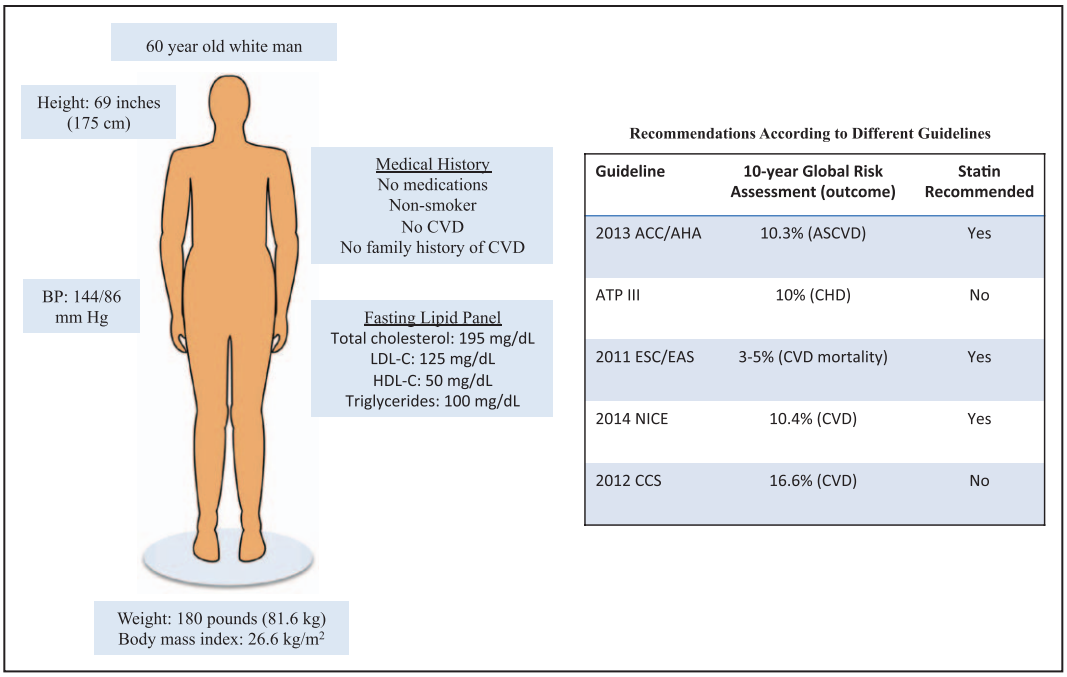

Recommendations According to Different Guidelines

Guideline	10-year Global Risk Assessment (outcome)	Statin Recommended
2013 ACC/AHA	10.3% (ASCVD)	Yes
ATP III	10% (CHD)	No
2011 ESC/EAS	3-5% (CVD mortality)	Yes
2014 NICE	10.4% (CVD)	Yes
2012 CCS	16.6% (CVD)	No

Figure. Clinical vignette and recommendations according to different international guidelines. ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ATP III, Adult Treatment Panel III; BP, blood pressure; CCS, Canadian Cardiovascular Society; CHD, coronary heart disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; and NICE, National Institute for Health and Care Excellence.

heart disease (CHD), the 2013 ACC/AHA guideline expanded the focus to atherosclerotic CVD (ASCVD), including CHD, stroke, and peripheral arterial disease. The 2013 ACC/AHA task force used a new approach to assess available evidence, focusing on randomized, controlled trials and systematic reviews and meta-analyses of randomized, controlled trials. Furthermore, the new guideline differed from the previous iterations in its intended scope. Whereas the ATP III guidelines included a comprehensive topical review and recommendations for laboratory evaluation, clinical diagnosis, lifestyle interventions, and drug therapy, the 2013 ACC/AHA guideline focused on answering 3 critical questions: (1) What is the evidence for LDL-C and non–HDL-C goals in secondary prevention of ASCVD? (2) What is the evidence for LDL-C and non–HDL-C goals in primary prevention of ASCVD? (3) What are the effectiveness and safety of lipid-modifying drugs in the primary and secondary prevention of ASCVD?[11] An independent contractor selected the relevant studies to be reviewed for each critical question according to prespecified criteria. This methodology was designed to reduce bias and to ensure that lower-quality studies were not considered when the recommendations were formulated.

Risk Assessment Model

A new tool for global risk assessment was introduced with the 2013 ACC/AHA guideline.[11] The previous guidelines recommended using a modified Framingham Risk Score (FRS) to estimate the 10-year risk of myocardial infarction or CHD death. Criticisms of this model included the absence of stroke as an outcome and a lack of racial, ethnic, and geographic diversity in the derivation population. In response, the Pooled Cohort equations were derived with data from 4 National Heart, Lung, and Blood Institute–sponsored cohort studies—the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), the Coronary Artery Risk Development in Young Adults (CARDIA) study, and the Framingham Heart Study (FHS; including original and offspring cohorts)—with adjudicated clinical outcomes, including myocardial infarction, CHD death, and fatal or nonfatal stroke.[14] The risk factors meeting the criteria for inclusion in the multivariable model were age, sex, total cholesterol, HDL-C, systolic blood pressure, antihypertensive treatment status, diabetes mellitus, and current smoking status. Of these variables, only diabetes mellitus was not included in the modified FRS endorsed by the ATP III guidelines. Different multivariable models were constructed for white and black individuals, and caution was recommended when these equations were applied to other races and to adults outside the age range of 40 to 79 years.

Treatment Recommendations

The 2013 ACC/AHA guideline recommended treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) for 4 categories of individuals: (1) secondary prevention for those with established ASCVD, (2) primary prevention of ASCVD for those with LDL-C ≥190 mg/dL, (3) primary prevention of ASCVD for individuals with diabetes mellitus and LDL-C of 70 to 189 mg/dL, and (4) primary prevention of ASCVD for those without diabetes mellitus, with LDL of 70 to 189 mg/dL, but with an estimated 10-year absolute risk of ≥7.5% as assessed by the Pooled Cohort equations. For this fourth group especially, the guideline authors

emphasized the importance of shared decision making based on a detailed risk discussion between patient and clinician before the initiation of statin therapy.[15] This clinician-patient discussion should include an assessment of the potential benefit, possible adverse effects and drug-drug interactions, lifestyle changes, management of other risk factors, and of course patient preferences. Additionally, other factors that might affect net risk reclassification could be used to further inform the treatment decision; these include LDL-C ≥160 mg/dL or evidence of genetic dyslipidemia, elevated lifetime risk, family history of premature CVD, blood levels of high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index <0.9, or abnormal coronary artery calcium score (≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity). Individuals at intermediate risk (10-year absolute risk of 5%–7.4%) or low risk (10-year absolute risk <5%) could also be considered for statin therapy on the basis of patient preferences or perceived benefit based on additional factors such as those listed above.

Instead of setting specific LDL-C targets, the 2013 ACC/AHA guideline essentially suggested a fixed dose (or intensity) of statin for each risk category, with intended LDL-C reductions of 30% to 49% and ≥50% for moderate- and high-intensity statins, respectively. The authors also suggested that nonstatin medications could be considered for those at high risk (secondary prevention, diabetes mellitus, LDL-C ≥190 mg/dL) if they are intolerant of the recommended dose of statin or have an inadequate response to statins. Although specific LDL-C targets were not endorsed, the 2013 ACC/AHA guideline recommended monitoring of the plasma lipid levels to ensure adherence, therapeutic response, and safety.

In comparison, the ATP III guidelines recommended a "treat-to-target" strategy with specific LDL-C goals for each risk group. For primary prevention, the LDL-C goal was set at <100 mg/dL for high-risk individuals (10-year CHD risk >20%), <130 mg/dL for those at intermediate risk (10-year risk CHD risk, 10%–20%), and <160 mg/dL for low-risk individuals (10-year CHD risk <10%). The LDL-C goal for secondary prevention or primary prevention of CVD in those with diabetes mellitus was <100 mg/dL, with the option to target <70 mg/dL for those at highest risk of CVD.[12,13]

In summary, the most important differences between the 2013 ACC/AHA guideline and the ATP III guidelines are the introduction of the Pooled Cohort equations, the elimination of LDL-C treatment targets, and the lowering of the threshold at which statins should be considered to an estimated 10-year absolute risk of 7.5%. The differences between these 2 documents are summarized in Table 1. To provide further context for the 2013 ACC/AHA guideline, we next compare its recommendations with those from other leading international guidelines, as outlined in Table 2.

Clinical Vignette

With the Pooled Cohort equations, the patient in our clinical vignette would have an estimated 10-year absolute ASCVD risk of 10.3%, and moderate- to high-intensity statin therapy could be considered after a clinician-patient discussion of potential risk reduction, adverse effects, drug-drug interactions, and patient preferences. With the modified FRS endorsed by the ATP III guidelines, on the other hand, he would be considered at intermediate risk on the basis of an estimated 10-year absolute risk of CHD of 10%. Hence, his LDL-C target would be <130 mg/dL, and given his current LDL-C of 125 mg/dL, he would not receive statin therapy.

Notably, a white man was used for our representative clinical vignette. The difference in estimated risk between the Pooled Cohort equations and the FRS would be more pronounced if a black woman, for example, had the same risk factor profile. With the Pooled Cohort equations, she would have an estimated 10-year ASCVD risk of 7.4%, which is considerably higher than the 2% 10-year CHD risk estimated by the FRS.

2011 European Society of Cardiology/ European Atherosclerosis Society Guidelines

Methodology

The European Society of Cardiology/European Atherosclerosis Society "Guidelines for the Management of Dyslipidaemias"[16] (2011 ESC/EAS guidelines) are a comprehensive document addressing cardiovascular risk assessment, laboratory evaluation, lifestyle modifications, drug treatment, and the approach to specific clinical settings such as familial dyslipidemias. The ESC/EAS task force based its findings on a comprehensive review of the literature in which greater confidence was placed in the results of randomized, controlled trials but was inclusive of all study designs.

Risk Assessment Model

Similar to the 2013 ACC/AHA guideline, the 2011 ESC/EAS guidelines supported the routine use of global cardiovascular risk assessment for all adults without established CVD but endorsed the use of the Systemic Coronary Risk Evaluation (SCORE) risk assessment tool. The SCORE tool, derived by pooling data from cohort studies with participants in 12 European countries, is designed to estimate the 10-year risk of fatal CVD event.[19] The decision to include only fatal outcome events was based on the assessment that fatal events are more easily calibrated in different populations and are less likely than nonfatal events to be affected by local geographic variations in diagnosis and treatment.[19] The total CVD event rate (including nonfatal events) has been shown to be ≈3-fold higher than the fatal CVD event rate.[16] Variables included in the SCORE risk model include age, sex, systolic blood pressure, total cholesterol, and smoking status, and separate models are used for low- and high-risk European countries.

Treatment Recommendations

According to the 2011 ESC/EAS guidelines, patients are considered to be very high risk for documented CVD, type 2 diabetes mellitus, type 1 diabetes mellitus with target organ damage, moderate to severe chronic kidney disease (CKD), or estimated 10-year absolute risk of fatal CVD ≥10%. High-risk individuals are those with a 10-year risk of fatal CVD of 5% to 9.9% or marked elevations in risk factors such as familial dyslipidemia or severe hypertension. Moderate risk is defined as a 10-year risk of fatal CVD of 1% to 4.9%, and low risk is defined as an estimated 10-year risk of fatal CVD event <1%. Extrapolating from clinical trials, the task force recommended LDL-C goals of approximately <70 mg/dL (1.8 mmol/L) for

Table 1. Comparison of 2013 ACC/AHA and ATP III Guidelines for the Treatment of Blood Cholesterol

Criteria	2013 ACC/AHA Guideline[11]	2001 ATP III Guidelines[12] With 2004 Update[13]
Focus of primary prevention	ASCVD, including CHD, stroke, and peripheral arterial disease	CHD
Guideline scope	Limited to 3 critical questions: evidence for cholesterol goals in secondary prevention, evidence for cholesterol goals in primary prevention, and effectiveness and safety of lipid-modifying drugs	Comprehensive document, including literature review, diagnosis and evaluation, treatment, lifestyle changes, and special clinical settings
Evidence considered	Randomized, controlled trials and meta-analyses of randomized, controlled trials	Inclusive systematic review
Risk assessment tool	Pooled Cohort risk equations: End points: CHD death, nonfatal MI, fatal or nonfatal stroke Derivation sample: pooled data from 4 cohort studies Predictors selected in the multivariable model: age, sex, total cholesterol, HDL-C, systolic blood pressure, antihypertensive treatment status, diabetes mellitus, and current smoking status Additional considerations: separate models created for men and women and for whites and blacks	Modified FRS: End points: CHD death, nonfatal MI Derivation sample: mostly white population of European descent Predictors selected in the multivariable model: age, sex, total cholesterol, HDL-C, systolic blood pressure, antihypertensive treatment status, and current smoking status
Cholesterol treatment targets endorsed	No	Yes
Lipid-lowering therapy for primary prevention in those without diabetes mellitus	LDL-C ≥190 mg/dL: high-intensity statin LDL-C 70–189 mg/dL and: 10-y risk ≥7.5%: high-intensity statin after clinician-patient discussion 10-y risk <7.5%: can consider moderate-intensity statin after consideration other factors* and based on a clinician-patient discussion	LDL-C ≥190 mg/dL ≥2 clinical risk factors† and: High risk (10-y risk >20%) and LDL-C ≥100 mg/dL (≥70 mg/dL optional): statin Intermediate risk (10-y risk, 10%–20%) and LDL-C ≥130 mg/dL (≥100 mg/dL optional): statin Low risk (10-y risk <10%) and LDL-C ≥160 mg/dL: may consider statin
Lipid-lowering therapy for primary prevention in those with diabetes mellitus	LDL-C ≥70 mg/dL and: 10-y risk ≥7.5%: high-intensity statin 10-y risk <7.5%: moderate-intensity statin	LDL-C ≥100 mg/dL: statin LDL-C ≥70 mg/dL with high risk features (optional): statin
Lipid-lowering therapy for secondary prevention	High-intensity statin	If LDL-C ≥100 mg/dL (≥70 mg/dL optional): statin
Non–LDL-C targets	Not discussed	HDL-C and triglyceride targets discussed in detail
Specific recommendations for the elderly	Pooled Cohort risk equations not validated in age >79 y Consider lower-intensity statin if age >75 y	Modified FRS not validated in age ≥65 y Clinical judgment recommended in older adults

ACC/AHA indicates American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ATP III, Adult Treatment Panel III; CHD, coronary heart disease; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and MI, myocardial infarction.

*Other factors to consider include LDL-C ≥160 mg/dL, family history, high sensitivity C-reactive protein, coronary artery calcium score, ankle-brachial index, and lifetime risk.

†Clinical risk factors include male age ≥45 y, female age ≥55 y, family history of premature CHD, current smoking, hypertension (≥140/≥90 mm Hg or on antihypertensive medications), and high-density lipoprotein <40 mg/d.

very high risk, <100 mg/dL (2.5 mmol/L) for high risk, <115 mg/dL (3.0 mmol/L) for moderate risk, and <190 mg/dL (4.9 mmol/L) for low risk. Therefore, the 2011 ESC/EAS guidelines differ from the 2013 ACC/AHA guideline in the choice of risk assessment model, the estimated 10-year risk considered sufficient to warrant medical treatment, and the continued endorsement of specific LDL-C targets to guide therapy.

Clinical Vignette

According to the SCORE risk assessment tool, our patient has a 10-year estimated risk of CVD mortality of 5% if he lives in a high-risk European country and would be considered at high risk. If he lives in a low-risk country, however, his 10-year estimated risk of CVD death would be 3%, and he therefore would be considered at moderate risk. Regardless of his country of residence, statin treatment would be recommended, given the LDL-C targets of <100 mg/dL for high-risk and <115 mg/dL for moderate-risk individuals.

2014 National Institute for Health and Care Excellence Guidelines

Methodology

The guidelines for lipid modification from the National Institute for Health and Care Excellence (NICE) in England were last updated in 2014.[17] The NICE guidelines are similar in scope to the 2013 ACC/AHA guideline, with recommendations for the primary and secondary prevention of CVD. Of the international guidelines reviewed, the NICE guidelines are noteworthy for the specificity of the drug recommendations provided and for the extent to which cost-effectiveness analyses are used to justify the recommendations.

Risk Assessment Model

The NICE guidelines support the use of the QRISK2 risk assessment tool for global cardiovascular risk assessment in all adults <84 years of age who are free of CVD. The QRISK2

Table 2. Comparison of International Guidelines for the Treatment of Blood Cholesterol

Criteria	2013 ACC/AHA Guideline[11]	2011 ESC/EAS Guidelines[16]	2014 NICE Guidelines[17]	2012 CCS Guidelines[18]
Evidence considered	Randomized, controlled trials	Comprehensive literature review	Comprehensive literature review	Comprehensive literature review
Risk assessment tool	Pooled Cohort equations	SCORE risk assessment tool	QRISK2 risk assessment tool	FRS for total CVD
End points	CHD death, nonfatal MI, fatal or nonfatal stroke	CHD death or fatal stroke (total CVD events is ≈3-fold higher than fatal event rate)	CHD death, CHD (MI or angina), stroke, or transient ischemic attack	CHD death, MI, coronary insufficiency, angina, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral artery disease, heart failure
Derivation sample	Pooled data from 4 cohorts	Pooled data from 12 European countries	British population, updated annually	Mostly white population of European descent
Predictors selected in the multivariable model	Age, sex, total cholesterol, HDL-C, systolic blood pressure, antihypertensive treatment status, diabetes mellitus, and smoking status (separate models created for whites and blacks)	Age, sex, total cholesterol, systolic blood pressure, and smoking status (separate models for high- and low-risk countries)	Age, sex, total cholesterol, HDL-C, systolic blood pressure, hypertension treatment status, diabetes mellitus, smoking status, ethnicity, family history of CHD, body mass index, socioeconomic deprivation, rheumatoid arthritis, CKD, and atrial fibrillation	Age, sex, total cholesterol, HDL-C, systolic blood pressure, antihypertensive treatment status, diabetes mellitus, and smoking status
Cholesterol treatment targets endorsed	No	Yes (LDL-C) Consider ApoB or non–HDL-C as alternative target	No	Yes (LDL-C) Consider ApoB and non–HDL-C as alternative target
Lipid-lowering therapy for primary prevention in those without diabetes mellitus	LDL-C ≥190 mg/dL LDL-C 70–189 mg/dL and: 10-y risk ≥7.5% after clinician-patient discussion 10-y risk <7.5% after consideration of other factors and based on clinician-patient discussion	LDL-C ≥190 mg/dL LDL-C <190 mg/dL and: 10-y risk ≥10% Moderate to severe CKD LDL-C ≥100 mg/dL and: 10-y risk 5%–9.9% Severe risk factors LDL-C ≥115 mg/dL and 10-y risk 1%–4.9%	10-y risk ≥10% or CKD	LDL-C ≥190 mg/dL LDL-C <190 mg/dL and 10-y risk 5%–9% (optional) LDL-C ≥130 mg/dL and 10-y risk 10%–19% LDL-C ≥75 mg/dL and: 10-y risk ≥20% CKD or proteinuria High-risk hypertension*
Lipid-lowering therapy for primary prevention in those with diabetes mellitus	LDL-C ≥70 mg/dL	Type 2 diabetes mellitus and LDL-C ≥100 mg/dL High-risk type 2 diabetes mellitus† and LDL-C ≥70 mg/dL Type 1 diabetes mellitus and target organ damage	Type 2 diabetes mellitus and 10-y risk ≥10% Type 1 diabetes mellitus and age >40 y, duration of disease >10 y, nephropathy, or CVD risk factors	Age ≥40 or <40 y and duration of disease >15 y, or age >30 y with microvascular complications
CKD considered a high-risk feature	No	Yes	Yes	Yes
Specific recommendations for the elderly	Pooled Cohort risk equations not validated for age >79 y Consider lower-intensity statin	SCORE validated for ages 40–65 y Clinician judgment urged in elderly	QRISK2 is calibrated to age ≤84 y	FRS to be used in age ≤75 y Clinical judgment urged in those >75 y
Additional considerations for risk assessment	Lifetime risk	Non–LDL-C targets	Non–LDL-C targets	Cardiovascular age and non–LDL-C targets

ACC/AHA indicates American College of Cardiology/American Heart Association; ApoB, apolipoprotein B; CCS, Canadian Cardiovascular Society; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; and SCORE, Systemic Coronary Risk Evaluation.

*High-risk hypertension is defined as hypertension plus 3 of the following risk factors: male, age >55 years, smoking, total cholesterol/HDL-C ratio >6, left ventricular hypertrophy, family history of premature CVD, ECG abnormalities, or microalbuminuria.

†High-risk type 2 diabetes mellitus is defined as diabetes mellitus plus 1 of the following risk factors: established CVD, CKD, age >40 years, and 1 or more cardiovascular risk factor or target organ damage.

model estimates the 10-year absolute risk of CHD (angina or myocardial infarction), stroke, or transient ischemic attack; is specifically calibrated to the British population; and is updated annually. Compared with the Pooled Cohort equations and SCORE risk assessment tool, the QRISK2 multivariable model includes additional risk factors such as ethnicity, family history of premature CHD, socioeconomic deprivation, body mass index, rheumatoid arthritis, CKD, and atrial fibrillation (in addition to age, sex, systolic blood pressure, total cholesterol, HDL-C, hypertension treatment status, diabetes mellitus, and smoking status, which are included in the Pooled Cohort equations).[20]

Treatment Recommendations

Similar to the 2013 ACC/AHA guideline, the 2014 NICE guidelines do not endorse a treat-to-target strategy. Instead, statin therapy is recommended for primary prevention in individuals with type 2 diabetes mellitus or those without diabetes mellitus but with an estimated 10-year absolute CVD risk of ≥10%. Statin therapy is also recommended for patients with type 1 diabetes mellitus who are >40 years of age with a disease duration of >10 years or with evidence of target organ damage. Atorvastatin 20 mg daily is recommended for primary prevention, and atorvastatin 80 mg daily is used for secondary prevention. In patients with CKD, 20 mg atorvastatin is suggested for both primary and secondary prevention.

Clinical Vignette

The patient in our clinical vignette has an estimated 10-year CVD risk of 10.4% with the QRISK2 model and would thus meet the criteria for statin therapy as primary prevention.

2012 Canadian Cardiovascular Society Guidelines

Methodology and Risk Assessment Model

The Canadian Cardiovascular Society (CCS) guidelines for the diagnosis and treatment of dyslipidemia for the prevention of CVD in adults were last updated in 2012 (2012 CCS guidelines).[18] The 2012 CCS guidelines recommend using the FRS for "total CVD" events to estimate the 10-year absolute risk. These guidelines also suggest doubling the estimated absolute risk for individuals with a family history of premature CVD on the basis of evidence of a 2-fold increase in CVD risk for FHS participants with a family history of premature CVD.[21] The authors of the 2012 CCS guidelines advise considering "cardiovascular age" in addition to estimated 10-year absolute risk when discussing lipid-lowering treatment with patients. "Cardiovascular age" and "heart age" may be easier concepts for patients to understand and may thereby facilitate shared decision making between patient and provider.[22]

Treatment Recommendations

The 2012 CCS guidelines endorse a treat-to-target strategy with primary prevention LDL-C targets of <75 mg/dL (2.0 mmol/L) for high-risk patients (10-year absolute risk ≥20%, CKD, or high-risk hypertension), <130 mg/dL (3.5 mmol/L) for intermediate-risk individuals (10-year absolute risk, 10%–19%), and <190 mg/dL (5 mmol/L) for those at low risk (10-year absolute risk <10%). A target LDL-C of <75 mg/dL is also recommended for those with diabetes mellitus and for secondary prevention, with a goal of <70 mg/dL (1.8 mmol/L) considered to be optional for those at highest risk.

Clinical Vignette

The patient in our clinical vignette has an estimated 10-year risk of total CVD of 16.6% according to the FRS and would be characterized as intermediate risk. The LDL-C target for the intermediate-risk group is <130 mg/dL. Therefore, he would not be recommended to receive statin therapy.

Comparison of International Guidelines

The 2013 ACC/AHA guideline differs substantially from its previous version, the ATP III guidelines, and other leading international guidelines. The effects of these changes were illustrated by our representative clinical vignette, in which the recommendations for initiating statin therapy for a 60-year-old man with modest cardiometabolic risk factors varied according to the guideline followed (Figure). The leading international guidelines included in this review differ in 3 key areas: the suggested risk assessment model (component risk factors and outcome evaluated), the threshold of risk considered sufficient to warrant initiating medical therapy, and the decision of whether to use a treat-to-target strategy.

Predicted Impact of Changes Proposed by the 2013 ACC/AHA Guideline

Dyslipidemia and cardiometabolic risk factors are highly prevalent in the population; therefore, changes to cholesterol treatment guidelines will affect the treatment recommendations for many people. Using data from the National Health and Nutrition Examination Surveys (NHANES), Pencina and colleagues demonstrated that ≈13 million American adults would be newly eligible for statin therapy with full implementation of the 2013 ACC/AHA guideline.[23] The increase in statin eligibility was attributable primarily to a higher proportion of individuals 60 to 75 years of age meeting criteria for treatment, which grew from 47.8% with the ATP III guidelines to 77.3% with the 2013 ACC/AHA guideline. The true impact of the 2013 ACC/AHA guideline is likely to be overestimated by these calculations, which assumed that all individuals in a statin benefit group would be treated with statins and therefore did not consider the effect of a clinician-patient discussion (emphasized by the new guidelines specifically) of the risks and benefits of statin initiation. Nevertheless, the 2013 ACC/AHA guideline is predicted to result in a higher number of statin-eligible individuals in the United States.

The overall impact of a larger proportion of the population receiving statin therapy is uncertain. Although overtreatment is a concern,[24] several recent studies have suggested that the 2013 ACC/AHA guideline aligns more closely than the ATP III guidelines with coronary atherosclerotic burden, as assessed by coronary artery calcium score and computed tomography angiography.[25,26] The features primarily responsible for the differences in statin allocation when the 2013 ACC/AHA guideline is compared with the ATP III guidelines are the risk assessment models used and the potential increase in statin assignment to lower-risk primary prevention.

Absolute Risk Estimation: A Comparative Critique

The Pooled Cohort equations were introduced alongside the 2013 ACC/AHA guideline with the goals of broadening ethnic and geographic diversity and incorporating stroke as an outcome in the risk prediction model.[14] Since their publication, several features of the Pooled Cohort equations have been criticized, including potential overestimation of absolute risk, dependence on chronological age, and derivation in older cohorts with reduced performance in more contemporary cohorts.

Absolute Risk Estimation

Overestimation of risk was first reported in the 2013 ACC/AHA guideline on the assessment of cardiovascular risk, during external validation with data from the more contemporary Multi-Ethnic Study of Atherosclerosis (MESA) and Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohorts, and with updated data from ARIC and FHS.[14] Several explanations for these findings were proposed. Foremost, a follow-up of at least 12 years was required for the derivation cohorts to accurately predict 10-year risk. Therefore, secular trends in statin use, revascularization procedures, or treatment of other risk factors such as hypertension and diabetes mellitus may account for the lower rates of CVD observed in more contemporary cohorts.[27–29] Underascertainment of clinically relevant events in the validation cohorts may also explain the apparent overestimation. In fact, when investigators used Medicare claims data to improve outcome ascertainment for the REGARDS study, they demonstrated improved performance of the Pooled Cohort equations.[28] However, concerns about the Pooled Cohort equations remain. Overestimation has repeatedly been demonstrated in several modern cohorts,[24,30,31] and in at least the Women's Health Study, the overestimation was not explained by differences in statin use, revascularizations, or underascertainment.[27] Despite these findings, it should be noted that the Women's Health Study was a primary prevention trial composed of clinical trial volunteers.[32] The lower risk observed in this study might therefore be partially attributable to a healthy volunteer effect.[33]

Although further investigation into the performance of the Pooled Cohort equations may be warranted, it is worth considering whether other existing risk prediction models perform better. This question is underscored by the observation that each of the leading international guidelines endorses a different risk assessment model. Unfortunately, systematic comparisons between risk prediction models are rare, and results are often conflicting, depending on the characteristics of the populations studied.[34] The FRS, for example, has been shown to both overestimate and underestimate risk in different populations.[35]

Model Performance Characteristics

Model calibration and discrimination are 2 features that can be used to assess the performance of risk prediction models. Calibration, estimated by the Hosmer-Lemeshow statistic, represents how well the predicted risk approximates the observed risk. Discrimination, measured by the c statistic, refers to how well the model distinguishes those who develop the disease from those who do not.[36] With data from the Rotterdam Study, investigators compared the performance of the Pooled Cohort equations, the modified FRS, and the SCORE risk assessment tool and determined that calibration was similarly poor among the 3 models, all of which significantly overestimated the risk of first CVD event.[24] Furthermore, discrimination was modest (highest with the SCORE tool) among the 3 models (c statistics ranging from 0.67–0.77).[24] Similarly, investigators from the MESA cohort evaluated the performance of 3 different FRSs, the Reynolds Risk Score, and the Pooled Cohort equations.[31] They found modest calibration for the 5 scores, with superior discrimination when the Reynolds Risk Score was used. Despite the differences demonstrated in the above studies, there is little consensus on the optimal risk prediction model.

Choice of Variables and Optimizing Models

The different risk prediction models endorsed by the international cholesterol guidelines vary little in terms of the risk factors included as predictors, with the QRISK2 model being noteworthy for incorporating additional variables. Future consideration could be given to assessing the desirability, appropriateness, and feasibility of establishing a more unified framework for estimating cardiovascular risk globally, perhaps by developing an international CVD risk prediction model. When data from international cohorts are combined, geographic, racial, and ethnic diversity can be optimized. The feasibility of this approach and the ability to calibrate a risk score to different countries were recently demonstrated.[37] Of course, there are several important hurdles to pursuing this approach globally. Primary among these is the lack of data for certain geographic and ethnic groups. For example, the so-called BRIC countries of Brazil, Russia, India, and China represent ≈40% of the world's population, but data on cardiovascular risk assessment in these countries are limited.[38] Furthermore, the degree to which individual risk assessment is affected by local characteristics that are not easily evaluated or integrated into risk prediction models is uncertain. These may include factors such as local environment, diet, climate, air pollution, built environment, cultural factors, availability of health care, and genetic background. With the representative patient in our clinical vignette, we observed important differences in the estimated risk using each of the 5 risk assessment models. Although these differences could be partially explained by specific model characteristics, the unique local factors may further contribute to variations in the weighting of variables, which could complicate direct comparison or harmonization of the different risk assessment models.

The 3 most important features of a risk prediction model are the covariates included, the outcomes modeled, and the time horizon. Optimization of each of these features may help further refine risk prediction techniques. As previously mentioned, most existing risk prediction models rely primarily on age, sex, cholesterol, blood pressure, hypertensive treatment status, diabetes mellitus, and smoking status. These individual measurements do not account for variations in lifetime exposure to risk factors. Because traditional cardiovascular risk factors generally lead to atherosclerosis over decades, it is

reasonable to hypothesize that the duration of exposure may be important. This approach is commonly used for cigarette smoking, which is recorded in pack-years of exposure, and there is evidence to support a similar approach with hypertension and dyslipidemia.[39–41] It is also notable that family history of premature CHD is included in the QRISK2 model and the modification of the FRS endorsed by the CCS but is not incorporated into the SCORE or Pooled Cohort equations models. Because, as cited by the 2012 CCS guidelines, there are data supporting a 2-fold increased risk in those with a family history of premature CVD,[21] it is intriguing that this variable did not meet the criteria for inclusion in certain models. Perhaps, it is related to how family history is defined or measured in the derivation cohorts. Although not included as a covariable in the Pooled Cohort equations model, the 2013 ACC/AHA guideline included family history of premature CVD as an important factor that can be considered when a risk decision is uncertain. In addition to improving how established risk factors are measured, discovery of new risk predictors (eg, using genomic data, biomarkers, and advanced imaging techniques) is an area of active investigation.

The optimal outcomes to include in a CVD risk prediction model remain uncertain. In particular, the inclusion of stroke in the Pooled Cohort equations has been questioned. Although CHD and myocardial infarction are almost exclusively caused by atherosclerotic disease, stroke is a heterogeneous disorder in which large-vessel atherosclerosis accounts for ≈40% of the disease burden.[42–44] Because blood cholesterol is directly related only to large-vessel atherosclerosis, using the same risk factors to predict CHD and stroke may be overly simplistic. In fact, low LDL-C has paradoxically been associated with a higher risk of hemorrhagic stroke in some studies.[45] Furthermore, it is well described that the incidence of stroke in the United States varies widely by geographic region, giving rise to the term stroke belt to refer to a grouping of 11 southeastern US states with age-adjusted stroke mortality rates that are 10% higher than the national average.[46] This area is not well represented in the 4 National Heart, Lung, and Blood Institute cohort studies used for the derivation of the Pooled Cohort equations. Therefore, using these equations to estimate the risk of stroke in the stroke belt will undoubtedly result in underestimation. Lastly, stroke disproportionally affects the elderly, with 17% of all stroke patients >85 years of age, an age group that is underrepresented in the discovery cohorts.[47] Therefore, including stroke as an outcome might reduce model precision and could further contribute to increased weighting of age in the risk prediction model.

Impact of Age on Absolute Risk Assessment

Indeed, the dramatic effect of age on estimated risk is an additional criticism of the Pooled Cohort equations, yet such age effects are observed to some extent in all of the previously mentioned risk prediction models. With the Pooled Cohort equations, many older adults may exceed the 7.5% estimated 10-year ASCVD risk threshold even in the absence of smoking, diabetes mellitus, hypertension, or dyslipidemia.[48] This feature is partially a result of the commonly used 10-year time window for risk prediction. The absolute event rate increases with age, as will the predicted risk. Therefore, approaches that are independent of chronological age such as estimating cardiovascular age or lifetime risk are appealing alternatives because the primary prevention of ASCVD during the life course, as opposed to during 10-year windows, is the ultimate aim. Reflecting this concept, the Pooled Cohort equations provide an estimated lifetime risk for individuals 20 to 59 years of age, and the 2012 CCS guidelines endorse the use of heart age in clinical decision making. However, further research is required to determine how best to apply these assessments in routine care and to develop an evidentiary basis for interventions driven by such estimates.

Thresholds for Initiating Statin Therapy

Whether a result of improved accuracy or of an overestimation of absolute risk, the Pooled Cohort equations partially explain the increase in statin-eligible adults with the 2013 ACC/AHA guideline. However, the decision to lower the threshold at which primary prevention statin treatment should be considered to an estimated 10-year absolute risk of ASCVD ≥7.5% is another crucial factor. In fact, this is the lowest threshold used by the international guidelines reviewed here. High-risk status was defined as an estimated 10-year risk of CHD >20% by the ATP III guidelines, fatal CVD ≥5% (equivalent to ≥15% for nonfatal events) by the 2011 ESC/EAS guidelines, CVD ≥10% by the 2014 NICE guidelines, and ≥20% by the 2012 CCS guidelines. It should be noted that because the outcomes included in the QRISK2 risk assessment tool endorsed by the NICE guidelines include softer diagnoses such as angina and transient ischemic attack, the 10% estimated risk by this calculation is likely to be qualitatively similar to the 7.5% absolute risk threshold of hard stroke and myocardial infarction events used by the 2013 ACC/AHA guideline. Furthermore, the decision to lower the threshold to 7.5% is supported by recent evidence demonstrating both the benefits of statin therapy in primary prevention trials including those with relatively low risk and very small adverse event rates in meta-analyses of statin trials including 170 000 participants.[49] In a meta-analyses by the Cholesterol Treatment Trialists' Collaboration, statin treatment in people with a low risk (<10%) of CVD resulted in an absolute reduction in major CVD events of 11 per 1000 over 5 years for each 39-mg/dL reduction in LDL-C, which greatly exceeded any observed hazard of statin therapy.[50] A Cochrane review of statin efficacy in primary prevention similarly found that the number needed to treat to prevent an adverse CVD event was 167 for those with an estimated 5-year risk of <5% and 67 for those with a 5-year risk of 5% to 10%.[51] Moreover, using microsimulation modeling, Pandya and colleagues[52] recently demonstrated that the 7.5% threshold is cost-effective, with an incremental cost-effectiveness ratio of $37 000 per quality-adjusted life-year gained.

In addition to increasing the number of statin-eligible adults in the United States, another important consequence of the lowering of the treatment threshold is a reduction in the proportion of individuals considered to be at intermediate risk, which would decrease from ≈32% to 12% with full implementation of the ACC/AHA guideline.[53] The most appropriate treatment for individuals at intermediate risk is, by definition, less certain; therefore, clinical judgment and additional testing

have historically been promoted for defining the treatment recommendations in this group. Significant attention has focused on developing and validating blood and imaging biomarkers to improve the precision of risk estimates for these individuals. By lowering the treatment threshold, the 2013 ACC/AHA guideline is proposing that the recent evidence, reviewed above, supports the use of statin therapy in most adults who were previously in the intermediate-risk category and therefore that the group of individuals in whom there is equipoise concerning the most appropriate treatment has diminished.

The international guidelines that we have reviewed endorse basing treatment decisions on estimated absolute CVD risk. However, recent publications have suggested potential modifications to these methods. Navar-Boggan and colleagues[54] have recently demonstrated the potential benefit of using age- and sex-specific 10-year risk thresholds to guide therapy, including raising the treatment threshold for adults 66 to 75 years of age to 10% in women and 15% in men. Alternatively, Ridker and colleagues[55] have proposed a hybrid algorithm that would incorporate clinical trial data into the primary prevention algorithm, although the superiority of this strategy is uncertain.[56] These strategies warrant additional investigation to determine whether they might be used to improve future cholesterol guidelines.

Treatment Targets for Lipid-Lowering Treatment

Another important modification introduced by the 2013 ACC/AHA guideline was the removal of specific treatment targets for lipid-lowering therapy. In explaining its rationale, the guideline committee referred to the absence of clinical trial data indicating what the precise targets should be, the lack of proven benefit for 1 target versus another, the inability to account for adverse effects of striving to achieve a given goal, and concern that target-based strategies may result in undertreatment with statins or overtreatment with nonstatins to reach these goals.[11] Additionally, there are small but significant differences between estimating LDL-C concentrations with the Friedewald formula and direct measurements.[57] Thus, with a treat-to-target strategy, the same patient might have different recommendations depending on the LDL-C assay used. On the other hand, critics of this "target-agnostic" approach have argued that treatment goals are valuable in clinical practice in that they serve to reinforce patients' positive behaviors and lifestyle changes and provide patients and their providers with tangible goals and metrics.[58] Furthermore, removing treatment targets makes it difficult for patients to improve their risk profiles (by nonpharmacological means) sufficiently to no longer warrant pharmacotherapy. Starting a preventive medication without the possibility of discontinuing the medication in the future may be a philosophical challenge from a public health perspective because it essentially medicalizes a large proportion of the community while de-emphasizing the potential importance of lifestyle modifications.

Although the most recent NICE guidelines similarly do away with treatment targets, the latest ESC/EAS and CCS guidelines continue to endorse treat-to-target strategies.[16,18] In the ESC/EAS and CCS guidelines, the justification for the continued use of cholesterol targets includes a number of primary and secondary prevention statin trials demonstrating improved outcomes with more intensive LDL-C lowering.[49,50,59–62] However, none of these trials used specific LDL-C targets to trigger medication dose adjustments, so LDL-C targets are extrapolated from these trials. This is a highly controversial area in which randomized, controlled trial data and everyday clinical practice appear to conflict. Innovative investigative techniques are needed to evaluate the effects of treat-to-target strategies on patient outcomes, incorporating the short-term effects of lipid lowering and the long-term effects related to patient well-being and encouraging healthy lifestyle behaviors.

Two developments since the publication of the 2013 ACC/AHA guideline may further complicate the target-agnostic approach. First is the publication of the results from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), which demonstrated a 2% absolute risk reduction of CVD events with ezetimibe added to statin therapy in patients after myocardial infarction.[10] Individuals receiving the combination of simvastatin and ezetimibe had lower average LDL-C levels (53.2 versus 69.9 mg/dL), suggesting that "lower is better" for LDL-C cholesterol, at least in the context of secondary prevention. The second development is the recent approval by the US Food and Drug Administration of 2 drugs from the new class of proprotein-convertase subtilisin/kexin type 9 inhibitors. While studies assessing the impact on hard CVD outcomes are ongoing, these drugs appear to be safe and effective in lowering LDL.[63] The IMPROVE-IT trial was the first to demonstrate the benefit of adding a nonstatin medication in patients already treated with statins for secondary prevention. As the options for nonstatin LDL-C–lowering medications proliferate, future guideline committees will be tasked with evaluating whether a return to LDL-C treatment targets (at least in certain circumstances) might be warranted to guide the addition of these new pharmacological options in certain high-risk patients already treated with statins.[64]

Primary Prevention Approaches for Those With Diabetes Mellitus or CKD

Despite variations in the language used and details about the suggested statin dose, the international guidelines generally agree on the approach to primary prevention in those with diabetes mellitus (Table 2 provides details). The notable differences pertain mostly to the treatment of patients <40 years of age, in whom there is scant evidence on the appropriateness of statin treatment for the primary prevention of CVD.

Agreement among the guidelines is less uniform for the treatment of individuals with CKD. The 2013 ACC/AHA guideline is alone among the international guidelines reviewed in not considering the presence of CKD to confer high risk. The 2011 ESC/EAS and 2012 CCS guidelines characterize patients with CKD as high to very high risk and recommend statin treatment to achieve the appropriate LDL-C targets.[16,18] The 2014 NICE guidelines recommend starting atorvastatin 20 mg for all patients with CKD.[17] The 2013 ACC/AHA, 2011 ESC/EAS, 2014 NICE, and 2012 CSS documents all agree that there is insufficient evidence to support specific recommendations for patients with end-stage renal disease receiving

regular hemodialysis. Although the 2013 ACC/AHA guideline is unique among the international guidelines reviewed in not treating all individuals with CKD as high risk, using data from the REGARDS study, Colantonio and colleagues[65] demonstrated that only 8% of individuals with CKD who are 50 to 79 years of age would not qualify for consideration of statin therapy on the basis of the 2013 ACC/AHA guideline. Therefore, whether this distinction between the 2013 ACC/AHA and other guidelines actually affects individual-level recommendations is uncertain.

Other Recent US Guidelines

Since the publication of the 2013 ACC/AHA guideline, the US Preventive Services Task Force (USPSTF)[48] and National Lipid Association (NLA)[66] have released recommendations for CVD prevention. Agreement between the recommendations from the USPSTF draft statement (which focuses on primary prevention) and the 2013 ACC/AHA guideline is generally strong. The USPSTF recommendations support the use of the Pooled Cohort equations for absolute risk assessment and suggest matching the intensity of statin therapy to absolute risk (as opposed to the treat-to-target approach of other guidelines). One notable difference, however, is that the USPSTF recommendations require individuals to have a 10-year risk of ASCVD of ≥10% (as opposed to ≥7.5%) and at least 1 cardiovascular risk factor to qualify for statin initiation. For those with an estimated 10-year ASCVD risk of 7.5% to 10%, the USPSTF states that low- to moderate-dose statins may be considered for individuals with additional risk factors or after a discussion with the patient about the relatively small absolute risk reduction expected in this group.[48] This distinction between the USPSTF statement and the 2013 ACC/AHA guideline highlights several important issues previously raised in this review, including the uncertainty of current risk prediction methods and difficulties balancing the considerable costs and potential adverse effects associated with statin use with the small absolute risk reduction in individuals with an estimated absolute 10-year ASCVD risk of <10%.

In contrast, the NLA guidelines differ substantially from the 2013 ACC/AHA guideline.[66] The NLA emphasizes counting risk factors as opposed to absolute risk assessment as the primary means of assigning risk categories, with absolute risk to be calculated only in those with 2 major risk factors. The NLA guidelines consider high risk to be an estimated 10-year ASCVD risk of ≥15% (using the Pooled Cohort equations). Furthermore, the NLA guidelines also endorse a treat-to-target strategy and support the use of treatment targets based on non–HDL-C as opposed to LDL-C. With these features, the NLA guidelines are more similar to the ATP III, 2011 ESC/EAS, and 2012 CCS guidelines than the 2013 ACC/AHA guideline.

Summary

The 2013 ACC/AHA guideline for cholesterol treatment made several notable changes to the older ATP III guidelines. Of these, the 3 most impactful are introducing the Pooled Cohort equations as the preferred risk assessment tool, lowering the risk threshold for considering statin in primary prevention settings (beginning with a clinician-patient discussion) to a 10-year absolute ASCVD risk of 7.5%, and removing cholesterol treatment targets. After reviewing several leading international guidelines, we observe a lack of consensus on the optimal approach to risk assessment, treatment thresholds, or the use of cholesterol targets among these guidelines. As a result, the recommendations for primary prevention lipid-lowering therapy for an individual vary according to which guideline is followed, as illustrated by the clinical vignette. These observations underscore the importance of further investigation aimed at refining risk prediction models and determining the optimal strategies for monitoring and adjusting medical therapy.

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Disclosures

None.

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