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Review

Recent AHA/ACC guidelines on cholesterol management expands the role of the clinical laboratory

Jing Cao[a,b], Sridevi Devaraj[a,b,*]

[a] Department of Pathology & Immunology, Baylor College of Medicine, Houston, TX, United States of America
[b] Department of Pathology, Texas Children's Hospital, Houston, TX, United States of America

ABSTRACT

The American Heart Association (AHA) and American College of Cardiology (ACC) recently published new guidelines for managing blood cholesterol. Five years from the publication of Pooled Cohort Equation to estimate 10-year risk of atherosclerotic cardiovascular disease (ASCVD), the newest guidelines put more focus on individualized risk assessment which necessitates increased participation of laboratory medicine in the prevention and management of ASCVD.

This mini-review summarizes key ideas from the new guideline that influence laboratory practice, including the renewed low-density lipoprotein cholesterol (LDL-C) treatment targets in primary and secondary prevention, the use of non-fasting lipids, new calculations of LDL cholesterol, and recommendations on assessing risk-enhancing factors in certain populations to aid the decision on statin and non-statin therapy. The shift in strategies for monitoring and lowering LDL-C has created opportunities for clinical laboratorians to more actively contribute to better identification of individuals at risk for ASCVD and partner with physicians taking care of the patient.

1. Background

Our understanding of atherosclerotic cardiovascular disease (ASCVD) risk factors was founded by the Framingham Heart study [1]. This influential investigation started in 1948 following 5209 participants and is now in the third generation. Traditional risk factors identified include smoking, hypertension, diabetes, and blood cholesterol. In order to tackle the modifiable risk factors and reduce morbidity and mortality of ASCVD, the National Heart, Lung and Blood Institute (NHLBI) initiated the National Cholesterol Education Program (NCEP) and has been issuing the Adult Treatment Panel (ATP) I through III from 1985 to 2004 [2–4]. More recently, NHLBI partnered with American Heart Association (AHA) and American College of Cardiology (ACC) by providing evidence based assessment of clinical trial results and publishing guidelines for lifestyle, risk assessment, cholesterol, and overweight and obesity.

The first set of AHA/ACC guidelines were published in November 2013 [5], mainly based on evidence from randomized controlled trials. In contrast to the last update of ATP III released in 2004 that made LDL-C the centerpiece for primary and secondary prevention of ASCVD, the 2013 ACC/AHA guideline recommended statins as the sole therapy for ASCVD risk reduction without defining target levels of LDL-C. Dosing of the therapy was guided by the pooled cohort 10-year risk assessment equation. This guideline has been questioned for its potential mis-estimation of risk, overuse of statin and lack of efficacy evaluation for lipid- lowering therapies. In November 2018, a new guideline on managing blood cholesterol was published by AHA/ACC [6], which is the focus of this mini-review.

2. Key features of the 2018 AHA/ACC guideline that pertain to the laboratory

2.1. New era for monitoring lipid levels

As a major modifiable risk factor, LDL-C has been a renewed focus of the 2018 cholesterol guidelines. The new guideline no longer limits its evidence source to randomized controlled trials, and has reviewed large scale observational cohort studies worldwide. The LDL-C targets for treatment and cholesterol management are not the focus of this mini-review, and the readers should refer to the guidelines [6] for risk stratifications and their corresponding managements and LDL-C target levels in different populations.

One of the benefits that arose from the new guidelines is the adoption of non-fasting lipids in general population screen [7], which greatly improves the availability and success rate of lipid screen orders, particularly in non-adult populations. In addition to the traditional Friedewald equation for calculating LDL-C, the 2018 guidelines also promote the use of the Martin/Hopkins LDL-C calculation method, which replaces the fixed factor of five used for the triglyceride to VLDL-C ratio with patient-specific variable factors [8]. Recent analyses have

* Corresponding author at: Clinical Chemistry, Texas Children's Hospital, 6621 Fannin St, Houston, TX 77030, United States of America
E-mail address: sxdevara@texaschildrens.org (S. Devaraj).

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shown that the Friedewald equation is prone to inaccuracy in the modern treatment era at low-LDL-C and high triglyceride levels. The Martin/Hopkins equation demonstrates superior accuracy in these settings and furthermore is acceptable to perform in the non-fasting setting, which confers additional benefits of convenience for patients and laboratories, although caution is needed in applying the Martin/Hopkins method in pediatric populations of LDL-C < 70 mg/dL and TG 150–400 mg/dL [9]. New equations need to be explored in different populations, especially with the use of the newer non statin therapies.

2.2. Emphasis on heart healthy lifestyle from younger age

Not only the methodology for assessing/calculating LDL-C was modernized, the 2018 guideline also expanded the target population of lipid screening. Healthy lifestyle has been advocated in ATP III and in the 2013 AHA/ACC guidelines which limits the impacted age group to 40–75 years. The new guideline specifically promotes assessment of lifetime risk in young adults below the age of 40, and emphasizes comprehensive and intensive lifestyle improvements to prevent development of the metabolic syndrome. For all patients at all visits the guideline encourages healthy diet and exercise in order to prevent and mitigate obesity, hypertension and hypercholesterolemia.

The new guideline recognizes that high cholesterol at any age has cumulative effect over the full lifespan. On the basis of a healthy lifestyle, it is important to be aware of the risk of high cholesterol levels and get treatment as appropriate at all ages to reduce the lifetime risk of heart disease and stroke. The new guideline suggests elective cholesterol screening is appropriate for children as young as two who have a family history of heart disease or high cholesterol. In most children, an initial non-fasting lipid screening test can be considered between the ages of 9 and 11 and then again after puberty between 17 and 21. The recommended age-stratified desirable lipid levels in children and adolescents are in alignment with the Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents from the NHLBI in 2011 [10].

2.3. Risk assessment tool

The pooled cohort 10-year risk equation remains the designated tool for physicians to make decisions on initiating lipid-lowering therapy [5]. Four major categories of patients are considered candidates for primary or secondary prevention. Primary prevention candidates include patients with no clinical ASCVD or diabetes, with LDL-C ≥ 70 mg/dL and 7.5% or greater 10-year risk as calculated by the pooled cohort equation, and patients with no clinical ASCVD but with diabetes and LDL-C ≥ 70 mg/dL. Secondary prevention candidates are patients with clinical ASCVD without heart failure. In addition, patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) are considered for high intensity statin therapy without calculating 10-year risk. Non-fasting lipid screen is recommended in primary prevention and followup with fasting lipid testing is indicated in subjects with abnormal initial screen results. In addition to traditional risk factors such as smoking, high blood pressure and high blood sugar, the new guideline adds factors like family history and ethnicity, as well as certain health conditions such as metabolic syndrome (including laboratory measurements of triglyceride, TG, high density lipoprotein-cholesterol, HDL and glucose), chronic kidney disease (creatinine and estimated glomerular filtration rate, eGFR), chronic inflammatory conditions (high sensitivity C reactive protein, hsCRP), premature menopause (follicle stimulating hormone, FSH) or pre-eclampsia and high lipid biomarkers other than cholesterol, to help health care providers better determine individualized risk and treatment options. They also recommend coronary artery calcium scores as a second-line decision-making tool with patients when determining whether to use statins.

2.4. Risk stratification for primary prevention in patients with indeterminate risk

The updated guidelines offer additional risk-assessment strategies to prevent unnecessary or insufficient prescribing. First, the clinician should assess for major risk factors such as hypertension, active or significant prior smoking and HbA1c, as these may change the risk-benefit conversation for patients. Since the adoption of HbA1C as a diagnostic criterion of diabetes mellitus, analytical performance of HbA1C has been under tight regulation [11]. Currently the College of American Pathologists expects HbA1C assays across manufacturers and laboratories to be within ± 6% of the National Glycohemoglobin Standardization Program (NGSP) target, with a planned move to ± 5% in 2019 [12], which further improves accuracy in risk assessment. Next, it is important to assess for risk enhancing factors that would favor statin prescription in this population. In adults 40 to 75 years of age without diabetes mellitus and 10- year risk of 5%–19.9%, risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dl; metabolic syndrome (including measurement of TG and HDL-C); chronic kidney disease; history of preeclampsia or premature menopause (age.

< 40 years); chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic infection with human immunodeficiency virus); high-risk ethnic groups (e.g., South Asian); persistent elevations of triglycerides ≥175 mg/dl; and, if measured in selected individuals, apolipoprotein B (ApoB) ≥130 mg/dL, hsCRP ≥2.0 mg/L, ankle-brachial index < 0.9, and lipoprotein (a) [Lp(a)] ≥50 mg/dL. Younger patients with Type 1 and Type 2 diabetics (aged 20–39 years) are also evaluated for diabetes-specific risk enhancers, including long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes), albuminuria ≥30 μg albumin/mg creatinine, and eGFR < 0.9.

Compared to the 2013 AHA/ACC guidelines, several biomarkers are recommended to be measured in clinical practice for the first time. For example, cutoffs derived from observational studies including ApoB ≥130 mg/dl and Lp(a) ≥50 mg/dl were suggested to facilitate the decision on lipid-lowering therapy. These changes in American national recommendations were preceded by position statement from the American Association of Clinical Chemistry (AACC) [13] and consensus recommendations in Europe [14]. It provides opportunity for laboratories to become more involved in patient care, and on the other hand, also require the laboratory medicine community to take more responsibility in harmonizing assays for the universal cutoffs. The International Federation of Clinical Chemistry (IFCC) and AACC has spearheaded programs for hs-CRP, ApoB and Lp(a) in the last two to three decades [15–17]. Standardization of ApoB and hsCRP measurements to the IFCC reference materials have been implemented in the Food and Drug Administration review criteria for clinical laboratory assays, while the efforts to harmonize Lp(a) assays to reporting in particle number units instead of mass concentration are still in process [18]. More recent research progress on other biomarkers of atherogenic or anti- atherogenic particles, such as small dense LDL [19], lipoprotein particle number [20], and HDL particle number [21] were not addressed in the 2018 guideline.

3. Stronger support for selective use of adjunct non-statin medications for LDL-C reduction in high-risk patients

Another significant change in the 2018 guidelines is the return of numbers, advocating for use of LDL-C treatment thresholds to inform the need to add non-statin therapies (ezetimibe and PCSK9 inhibitors). In very high-risk ASCVD, a LDL-C threshold of 70 mg/dL is used to consider addition of nonstatins to statin therapy if tolerated. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL) that are on high-intensity statin therapy, if the LDL-C level remains ≥100 mg/dL, adding ezetimibe is considered reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL, and the patient has

Table 1
Summarizes the major changes from the 2013 to 2018 AHA/ACC guidelines on managing blood cholesterol to lower risk of ASCVD that pertain to clinical laboratories.

	2013 Guideline	2018 Guideline
Recommended universal lipid screen	Limited to Age > 40, with fasting lipid profile.	Assess lifetime risk of ASCVD in children as young as 9 years old with nonfasting lipids.
Method of cholesterol calculation	The Friedewald Equation.	Recommend Martin-Hopkins LDL-C formula at low LDL-C levels.
LDL-C target level to guide therapy	Not specified	Recommended for consideration of non-statin therapy
Risk enhancing factors in addition to the pooled cohort equation for primary prevention	LDL-C ≥ 160 mg/dL, hs-CRP ≥ 2.0 mg/L, ABI < 0.9, elevated lifetime ASCVD risk, family history of premature ASCVD.	Persistently elevated LDL-C ≥ 160 mg/dL, apoB ≥130 mg/dL, increased Lp(a), hsCRP ≥2.0 mg/L, low ABI (< 0.9), metabolic syndrome (TG > 150, or TG > 175 for non-fasting, HDL < 40 or 50), chronic kidney disease (Creatinine, eGFR), chronic inflammatory disorders (CRP), premature menopause (FSH), South Asian ancestry, family history of premature ASCVD.
Statin management in individuals with age of 40–75, diabetes and LDL-C 70–189 mg/dL.	Moderate or high intensity statin treatment option is based on estimated 10-year ASCVD risk.	Start moderate intensity statin without need to calculate 10-year ASCVD risk. If multiple risk factors or 50–75 years of age, reasonable to start a high intensity statin.

multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered. LDL-C testing is recommended 4 to 12 weeks after statin initiation or dose adjustment, and repeated every 3 to 12 months to assess adherence and percentage response to LDLC–lowering medications and lifestyle changes.

Overall, the new guidelines have much broader scope of risk factors, target population, and treatment options for preventing ASCVD, which enables clinical laboratories to be more actively involved in ASCVD risk identification and prevention (Table 1). With the increased availability of big data from both research studies and electronic medical records, laboratories are equipped with more robust tools to explore precision medicine in cardiovascular diseases [22].

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