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Deciphering Cholesterol Treatment Guidelines A Clinician's Perspective

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The publication of cholesterol treatment guidelines by the American College of Cardiology and the American Heart Association (ACC/AHA)[1] immediately met with considerable support as well some criticism related to their applicability in practice. The criticism was based primarily on 2 issues: eliminating numerical targets for low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non–HDL-C) and debate about the value of the new pooled risk calculator for treatment initiation decisions.[2,3] Several additional treatment guidelines from established organizations were published in the past year, including from the UK National Institute for Health and Care Excellence (NICE),[4] the National Lipid Association (NLA),[5] and, most recently, the American Diabetes Association (ADA).[6]

All of these current guidelines emphasize the need for life style changes and to intensify statin therapy as the highly preferred regimen in patients with established atherosclerotic cardiovascular disease (CVD) or those at very high risk of developing CVD. However, there are important differences in the criteria for risk assessment and treatment, particularly for primary prevention in the population with or without diabetes (Table). For instance, there are notable differences in approaches to patient selection and treatment proposed by the NLA, whereas the ADA endorses much of the ACC/AHA guidelines, with the major exception of type 1 diabetes, and NICE provides a unique perspective in certain areas. Despite these differences, each of these guidelines has considerable merit when making treatment decisions.

Screening and Risk Assessment

Both NICE and the NLA emphasize non–HDL-C as a treatment target. Therefore, a screening lipid profile does not require a fasting lipid assessment. For primary prevention, the ACC/AHA has recommended an age category of 40 to 75 years for risk assessment if LDL-C is less than 190 mg/dL, based on evidence from randomized trials. This is a point of contention in view of the strong epidemiologic and experimental evidence of the relationship between LDL-C level and atherosclerosis and challenges clinicians in efforts to reduce long-term CVD risk in younger patients with other cardiovascular risk factors. This

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is especially true for adult patients younger than 40 years with diabetes. The ADA has further categorized such patients and has recommended screening based on presence or absence of other risk factors (LDL-C>100mg/dL, high blood pressure, smoking, or body mass index above the normal range), regardless of the type of diabetes and without any mention of a lower age cutoff. Surprisingly, albuminuria is not included as a risk factor despite acknowledgment of its role in CVD.

NICE, however, refined indication for screening in type 1 diabetes if age is older than 40 years, duration of diabetes is longer than 10 years, or chronic kidney disease or other risk factors are present. The NLA recommends screening everyone aged 20 years or older and risk categorization based on number of risk factors, and places greater emphasis on other biomarkers in risk refinement. NICE has developed an updated QRISK2 that includes family history and chronic kidney disease in contrast to the ACC/AHA. Both guidelines recommend use of risk calculators for type 2 diabetes, whereas the NLA advises against using any risk calculator for diabetes. However, none of the risk calculators were validated in any randomized trials.

Lipid Targets and Recommendations

For patients with or at very high risk of atherosclerotic CVD, including having an LDL-C level greater than 190 mg/dL and/or familial hypercholesterolemia, there is concordance among all guidelines regarding need for intensive statin treatment, defined by the ACC/AHA as high-dose statin therapy designed to achieve LDL-C reduction of greater than 50% from baseline, without specific lipid goals. For primary prevention, the ACC/AHA and NICE recommend quantitative risk calculations and moderate-to high-intensity statin therapy, again designed to achieve a percentage LDL-C or non-HDL-C reduction, respectively. However, the NLA recommends a “lower is better” approach by risk category, with specific goals for non-HDL-C and LDL-C (and apolipoprotein B, particularly in the presence of the metabolic syndrome and in those with high triglyceride levels) based on extrapolations from meta-analysis of statin trials. Moreover, the NLA is more liberal in the use of nonstatin therapy, now supported by recent results from the IMPROVE-IT trial, in which addition of ezetimibe to statin therapy resulted in modest but significant reductions in CVD end points in line with additional LDL-C reduction.[7] This is of much interest to clinicians and patients, who are often challenged by difficulties with adherence to intensive statin therapy.

One of the main unanswered questions in primary prevention is when to start LDL-C-lowering treatment inindividual patients, especially those younger than 40 years and with other risk factors. Many such patients are at increased risk of events in the long term. Lifetime risk calculation has some value but is derived from limited data. For patients aged 40 years or older without diabetes, the ACC/AHA recommendation is to treat only if the 10-year risk exceeds 7.5% (with 5%-7.5% as an option if LDL-C >160 mg/dL or other markers of high risk are present). In contrast, all patients aged 40 years or older with type 2 diabetes and LDL-C levels greater than 70 mg/dL are candidates for a 30% to 50% LDL-C reduction regardless of other risk factors.

Similar questions and debate persist for primary prevention among patients aged 75 years or older. Because of lack of adequate evidence, the ACC/AHA guidelines have no recommendation for treatment in this large group with high rates of CVD events. However, the ADA, NICE, and the NLA make a good case for initiating therapy in the older population, more specifically those younger than 85 years in NICE.

Adherence to Treatment

Some have misconstrued the ACC/AHA position by assuming little need for lipid monitoring because there are no numerical lipid goals. Evidence exists for remarkable heterogeneity in LDL-C response to a given dose of statin therapy based on genetic background, ethnicity, sex, and concomitant drug therapy. In fact, lipid monitoring is essential in practice to guide adherence to ensure that the recommended percentage LDL-C reduction is being achieved and maintained. All guidelines recommend periodic lipid monitoring.

Conclusions

The publication of the ACC/AHA cholesterol guidelines was much needed to spark efforts to intensify statin treatment in a majority of the high-risk population, who have often been inadequately treated in the past. The publication of 3 other major guidelines during the past year should result in some revisions and updates in all guidelines to promote a more comprehensive approach to avoid both undertreatment and overtreatment as well as consideration of nonstatin therapy when needed.

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Table
Key Similarities and Differences Among Major Cholesterol Guidelines

	ACC/AHA (2013)	ADA (2015)	NICE (2014)	NLA (2014)
Risk assessment				
Screening	Fasting lipids	Fasting lipids	Fasting/nonfasting lipids	Fasting/nonfasting lipids
Eligibility for primary prevention if LDL-C <190 mg/dL	Age 40-75 y and LDL-C 70-189 mg/dL	Age >40 y (see exceptions)	Age 40-84 y (exception: type 1 diabetes)	Age ≥20 y and categorization (low, moderate, high, and very high risk)
10-y risk calculator for primary prevention	PRC	Not recommended	QRISK2 2014 risk calculator (except for type 1 diabetes)	If 2 major risk factors, FRS or PRC
10-y risk threshold for primary prevention	≥7.5%	None	≥10.0%	≥10.0% (FRS) ≥15% (PRC)
Lipid targets (with lifestyle therapy)				
ASCVD, FH, or LDL-C ≥190 mg/dL	High-dose statin; >50% reduction in LDL-C	High-dose statin; >50% reduction in LDL-C	High-dose statin	Non-HDL-C <100 mg/dL; LDL-C <70 mg/dL
Preferred treatment	Atorvastatin, 40-80 mg, or rosuvastatin, 20-40 mg		Atorvastatin, 80 mg	High-dose statin plus nonstatin treatment to achieve goal
Primary prevention if no FH and LDL-C <190 mg/dL				
Diabetes not present	Moderate-dose statin to lower LDL-C >30%-50%		Non-HDL-C reduction >40% (atorvastatin, 20 mg/d)	Non-HDL-C <130 mg/dLand LDL-C <100 mg/dL for low, moderate, or high risk
Diabetes present	Type 2 or type 1: moderate-dose statin if risk <7.5%; high-dose statin if risk ≥7.5%	If age 40-75 y, moderate-dose statin for 30%-50% reduction in LDL-C if no other risk factors; high-dose statin if additional risk factors If age <40 y and other risk factors, moderate- to high-dose statin	Type 2: same as above Type 1: same as above if age >40 y, duration >10 y, chronic kidney disease, or other risk factors	Type 2 or 1: non-HDL-C<100 mg/dL and LDL-C <70 mg/dL if ≥2 risk factors or end organ damage
Older adults	Not indicated if age >75 y	Same as above for age >40 y	If age <85 y, statin per QRISK2 assessment If age ≥85 y, consider statin but individualize	Not stated; follow risk categories as defined
Adherence to therapy	Initially at 4-12 wk, then every 3-12 mo (no goals for LDL-C or non-HDL-C)	Monitor as needed (no goals for LDL-C or non-HDL-C)	At 3 mo to assess non-HDL-C, then yearly	Every 4-12 mo to follow goals

Abbreviations: ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; FRS, Framingham risk score; non–HDL-C, non–high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; NLA, National Lipid Association; PRC, pooled risk calculator.