Is There an Ideal Low-Density Lipoprotein Cholesterol Level? Confusion regarding Lipid Guidelines, Low-Density Lipoprotein Cholesterol Targets, and Medical Management

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Abstract

Keywords

- ▶ acute coronary syndrome
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There are multiple guidelines for managing patients with high-risk cardiovascular disease, and unfortunately for the practicing clinician, these guidelines are quite variable. Some are fairly specific whereas others are not, resulting in a great deal of confusion regarding whether management of low-density lipoprotein cholesterol (LDL-C) should be tailored only, targeted only, or managed by a combination of both. In the management of cardiovascular disease, favorable cardiovascular outcomes can be obtained by simply lowering the LDL-C in the absence of any other medications. The advent of statins, the most potent LDL-C-lowering medication yet when developed, provided benefits augmented by the presence of multiple pleiotropic effects. Tailoring and/or targeting the decrease in LDL-C is also an issue of concern. Then, in 2016, the new proprotein convertase subtilisin-like/kexin type 9 (PCSK9) inhibitors appeared, providing a solution to patients with high-risk cardiovascular disease with statin intolerance and those who did not attain a desired LDL-C level while on a high-dose statin. These new PCSK9 inhibitors necessitate a determination of how low the LDL-C can and should go, most likely safely down to a beneficial level of 25 mg/dL for the highest-risk patient. These issues are documented and discussed with an attempt to help the reader make an informed risk management decision.

The existence of multiple lipid management guidelines along with periodic changes made to some of those guidelines has led to much confusion including a recent guideline authored by the United States Department of Veterans Affairs and Department of Defense (VA/DoD).¹ This review discusses the recommendation and issues surrounding these varied guidelines, relates them to clinical practice, and considers how the individual clinician can use them in combination with a tailored approach to each patient with an individually associated low-density lipoprotein cholesterol (LDL-C) target.

Confusion Regarding Lipid Guidelines

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline for the management of

blood cholesterol deals with cardiovascular risk reduction by focusing on four groups that appear to benefit from treatment with a high-dose statin.^{2–4} The goal of treatment with the high-dose statin is to attain a “significant” LDL-C reduction of $\geq 50\%$ from the untreated baseline without specifying a specific LDL-C target. The four groups that the ACC/AHA guidelines focus on are as follows (▶ **Table 1**): established clinical cardiovascular disease; a documented LDL-C of ≥ 190 mg/dL; the presence of diabetes mellitus (DM) in a patient aged 40 to 75 years without clinical cardiovascular disease and LDL-C 70 to 189 mg/dL; and patients with an absence of clinical cardiovascular disease or DM with LDL-C range of 70 to 189 mg/dL, but who have a computer-analyzed cohort equation estimated 10-year cardiovascular risk of $\geq 7.5\%$.^{2–4}

Table 1 Summary of 2013 ACC/AHA guideline for treatment of blood cholesterol²⁻⁴

Cardiovascular risk focused on four groups that appear to benefit from a statin. ²⁻⁴ 1. Established clinical cardiovascular disease. 2. Documented LDL-C ≥190 mg/dL. 3. Presence of DM in patient aged 40–75 y without clinical cardiovascular disease and LDL-C 70–189 mg/dL. 4. Absence of clinical cardiovascular disease or DM, LDL-C 70–189 mg/dL, and estimated 10-y cardiovascular risk ≥7.5%.
Goal is to use high-dose statin to attain a “significant” LDL-C reduction of ≥50% from the untreated baseline without specifying a specific LDL-C target. ²⁻⁴
Estimation of 10-y cardiovascular risk by internet cohort equations. ²⁻⁴

Abbreviations: ACC, American College of Cardiology; AHA, American heart Association; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.

In contrast, various organizations have offered differing blood cholesterol guidelines since the ACC/AHA 2013 guideline is not universally accepted (►Table 2). The International Atherosclerosis Society in 2014 recommended that the optimal LDL-C is < 100 mg/dL for primary prevention with LDL-C < 70 mg/dL for secondary prevention.⁵ Both the American Association of Clinical Endocrinologists (AACE)⁶ and the National Lipid Association (NLA)⁷ are opposed to removing LDL-C goals, in contrast to the 2013 ACC/AHA recommendation. For very high cardiovascular risk, LDL-C < 70 mg/dL is the recommendation of both the AACE and NLA. The European Society of Cardiology and the European Atherosclerosis Society both recommend LDL-C < 70 mg/dL for the patient with very high-risk cardiovascular disease.⁸ However, adding further confusion, the VA/DoD recently published another set of lipid management guidelines.¹ The VA/DoD guidelines now call for only a moderate-intensity statin in patients even with a 10-year cardiovascular disease risk of ≥12%, a high-dose statin in only patients with recent acute coronary syndrome (ACS) or recurrent cardiovascular disease events on a moderate-intensity statin, no analysis of surrogate cardiovascular risk markers such as high-sensitivity C-reactive protein/coronary calcium score, and no follow-up of LDL-C while being treated.¹

Such markedly differing guidelines highlight the problem practicing clinicians face when trying to gather the very best information possible for the benefit of their patients. Furthermore, a large percentage of clinicians still do not pay attention to acceptance of the lipid hypothesis, which states that increased total cholesterol and increased LDL-C are both associated with increased cardiovascular risk. In a study of 21 U.S. practice locations, Virani et al showed that approximately 50% of

providers, including specialists as well as nonspecialists, had not read the 2013 ACC/AHA guideline and were unable to risk-stratify patients.⁹ Only 40.4% in practice followed a protocol of repeating a lipid panel 6 to 8 weeks after beginning a statin regimen in a patient who had suffered a recent myocardial infarction.⁹ This survey demonstrates that guidelines do not reach many practitioners where “the rubber meets the road,” that many academics/investigators creating these guidelines are not aware of this reality, and how important it is to keep goals and recommendations as simple as possible with easily recognized and acceptable targets.

Confusion regarding Low-Density Lipoprotein Cholesterol Targets

Targeting LDL-C in the management of cardiovascular risk has recently been contested. Hayward and Krumholz stated in an Editor’s Perspective article that the scientific basis for treating to an LDL-C target does not exist.¹⁰ Their contention was that no major randomized clinical trial has specifically evaluated cardiovascular risk benefit related to a specific LDL-C target. These authors advocated a “tailored” treatment as simpler, safer, more effective, and, furthermore, as a more evidence-based approach.¹⁰ The 2013 ACC/AHA guideline added to this confusion as no desired LDL-C target was specified.²⁻⁴ Further confusion was added by Hofer et al in 2016 who stated that available new clinical evidence reinforced the importance of cardiovascular risk and the secondary importance of LDL-C levels.¹¹ Unfortunately, such statements completely ignore well-established clinical evidence-based medicine such as the almost 30-year-old report of Blankenhorn et al, which showed coronary artery regression by quantitative coronary

Table 2 Summary of the blood cholesterol treatment guidelines of other interested special organizations

International Atherosclerosis Society recommends LDL-C < 70 mg/dL for secondary prevention. ⁵
AACE is opposed to removing LDL-C goals. ⁶
NLA is opposed to removing LDL-C goals. ⁷
ESC supports LDL-C < 70 mg/dL for the very high-risk cardiovascular patient. ⁸
The European Atherosclerosis Society supports LDL-C < 70 mg/dL for the very high-risk cardiovascular patient. ⁸
The Veterans Administration/DoD recommends high-dose statin only in patients with recent ACS or recurrent cardiovascular disease events on a moderate-intensity statin. ¹

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACS, acute coronary syndrome; DoD, Department of Defense; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; NLA, National Lipid Association.

artery angiography in the Cholesterol-Lowering Atherosclerosis Study (CLAS) associated with a 43% LDL-C reduction by colestipol-niacin treatment.^{12,13} Similar to CLAS are the ileal bypass studies by Buchwald et al 25 plus years ago, which demonstrated a significant decrease in cardiovascular risk in association with a significant LDL-C reduction.^{14,15} These studies by Blankenhorn et al^{12,13} and Buchwald et al^{14,15} are basically pure plays in LDL-C reduction without the benefit of significant pleiotropic effects associated with statins¹⁶ or proprotein convertase subtilisin-like/kexin type 9 (PCSK9) inhibitors.¹⁷ Another pure play in low LDL-C levels are patients with hypobetalipoproteinemia as a specific familial condition defined by an LDL-C equal to or less than the 5th percentile.¹⁸ In mg/dL, LDL-C levels in hypobetalipoproteinemia can be seen in the 30s and 40s. Affected individuals have some variable noncardiovascular medical problems but below-average risk for cardiovascular disease, further supporting a cardiovascular advantage for diminished LDL-C levels.¹⁸ Data reported by Grundy et al illustrating a log-linear relationship between LDL-C levels and relative risk for coronary artery disease (CAD) showed a linear decrease in CAD relative risk down to an LDL-C level of 40 mg/dL.¹⁹

Therefore, there is ample evidence to support the value of LDL-C reduction to decrease cardiovascular risk. The question then becomes why create confusion regarding targeting or tailoring, especially when the reality is that acceptance of the 2013 ACC/AHA guideline is poor, 50% of medical practitioners have not read the guideline, and adherence to the guideline is limited.⁹ Because of this, it is appropriate to tailor the targeting of LDL-C levels to individual patients as initial levels vary and much remains to be learned regarding unknown factors in the development of atherosclerosis. Therefore, why not, based on the starting LDL-C level and associated risk, tailor an approach to each patient, which would include a different LDL-C target depending on risk and baseline LDL-C levels?²⁰ Simplicity and consistency are essential when trying to convince physicians and other practitioners to manage an evidence-based problem. It is concerning that many high-risk referrals are not given any medication for elevated LDL-C levels.

Another issue regarding LDL-C is—how low is too low. The newborn infant has an LDL-C level of approximately 30 mg/dL.²¹ Decreases in the LDL-C to 50 mg/dL in adults have been associated with plaque regression with associated safety.²² In incidences of ACS, patients in one study with LDL-C < 40 mg/dL, LDL 40 to 60 mg/dL,²³ and in another study with LDL-C < 50 mg/dL²⁴ all had fewer adverse cardiovascular events. A decrease in the LDL-C to 25 mg/dL appears to be safe for at least 1 year²² and findings suggest that this level is adequate to nourish the body indefinitely with cholesterol.²¹

Evidence-Based Medical Management of Coronary Artery Disease

Statins as the Basic Medical Management

Although decreasing cardiovascular risk by lowering LDL-C by any means appears beneficial, statins remain the treatment of choice when tolerated by the patient. Multiple outcomes studies show significant decreases in cardiovascular events

in response to statins for both primary²⁵ and secondary^{26–30} cardiovascular disease prevention. As long as a statin is tolerated, this class of medications should be the starting point for cardiovascular risk reduction, both primary and secondary, due to the proven outcomes studies, the benefit in lowering LDL-C, and the beneficial pleiotropic effects of statins.¹⁶ Unfortunately, many patients do not tolerate statins due to symptoms of myopathy and this is not a mere 1 to 2% of patients as sometimes claimed, but the realistic incidence is in the range of 10.5% of patients.³¹

Role of the New Proprotein Convertase Subtilisin-Like/Kexin Type9 Inhibitors

Because of the prevalence of increased cardiovascular risk and intolerance of many patients to statins, the recent availability of PCSK9 inhibitors has been an incredible boon for the management of patients with high-risk cardiovascular disease. PCSK9 decreases LDL-C receptor levels by binding to the LDL-C receptor.³² It therefore acts as a negative feedback control on the receptors, and when PCSK9 is bound to the receptors, LDL-C catabolism is diminished with a resultant increase in plasma LDL-C. The new medication class of PCSK9 inhibitors are monoclonal antibodies to the PCSK9 protein, they are administered by subcutaneous injection, and they are highly specific, resulting in up to a 72% reduction in LDL-C.³²

Because these PCSK9 inhibitors have some pleiotropic-like effects of statins,¹⁶ there may be a benefit far beyond a pure decrease in LDL-C. The PCSK9 protein itself increases atherosclerotic plaque vulnerability, has a proinflammatory effect, increases LDL-C oxidation, and promotes atherosclerotic plaque formation.¹⁷ The pleiotropic benefits of a PCSK9 inhibitor result from suppression of these undesirable effects. Relevant to these observations is that during ACS from myocardial ischemia, the PCSK9 protein increases, so that suppression by an inhibitor would appear to have significant pleiotropic benefit.¹⁷ The anti-inflammatory and plaque stabilization effects of PCSK9 inhibitors may ultimately necessitate immediate administration, just like a statin, to patients with ACS.¹⁷

These potent new PCSK9 inhibitors require a thorough understanding of appropriate LDL-C levels to tailor, target, and attain for each patient, and to understand how low the LDL-C can and should safely go. A very significant decrease in the LDL-C down to 25 mg/dL is probably safe.^{21,22}

Conclusion

The medical practitioner has to be aware of the multiple lipid guidelines in effect and realize that they are just that—guidelines that are the creation of supposed expert opinion but not an exact protocol that must be followed. Each practitioner must be capable of selecting the best information available and then be able to apply it as best as he or she can for the benefit of the patients entrusted to their care. If the 2013 ACC/AHA guideline is followed,^{2–4} the patient with high-risk cardiovascular disease will receive a high statin dose unless the patient develops statin intolerance. The 2016 VA/DoD guideline is even more nonspecific and nonchalant, recommending only a moderate-intensity statin in patients with

a 10-year cardiovascular disease risk of $\geq 12\%$ and a high-dose statin only in patients with recent ACS or recurrent cardiovascular disease events on a moderate-intensity statin.¹ Fortunately, other guidelines are more specific and recommend attaining an LDL-C level of < 70 mg/dL in patients with high-risk cardiovascular disease.⁵⁻⁸ In summary, each practitioner must take this information, critique it, try to understand the clinical problem, and then make his or her best possible clinical decision regarding a tailored approach with an LDL-C target for the patient. Unfortunately, a very high percentage of practitioners are far from this level of practice and variable guidelines have not helped improve the level of cardiovascular risk management.

Conflicts of Interest

The author has no conflicts of interest to declare involving any pharmaceutical company, any device company, or any funding agency.

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