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Chronic Diseases and Translational Medicine 2 (2016) 7–9

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Perspective

Amendment of the low-density lipoprotein cholesterol target in the 'Chinese Guidelines for the Prevention and Treatment of Adult Dyslipidemia': Opinion

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Received 27 April 2016
Available online 7 June 2016

Dyslipidemia, particularly the elevation of low-density lipoprotein cholesterol (LDL-C) levels, is the prerequisite for the occurrence and development of plaque-based atherosclerotic cardiovascular disease (ASCVD). LDL particles pass through the vascular endothelium and become lodged within the walls of blood vessels. Oxidative modification of LDL then occurs under the action of extracellular matrix molecules, followed by foam cell formation after macrophage phagocytosis. Subsequently, there occur localized biological responses, mainly non-specific inflammation, which further promotes LDL retention and atherosclerotic lesion progression.

A large number of clinical studies has repeatedly confirmed that, regardless of the medication type or intervention method, as long as the plasma LDL-C level is reduced, atherosclerotic lesions can be stabilized, impeded, or alleviated. The ASCVD incidence as well as morbidity and mortality rates will also decrease significantly. Domestic and international dyslipidemia prevention guidelines have all emphasized that LDL-C plays a central and pathogenic role in ASCVD. Hence, the prevention and control of ASCVD risk by decreasing blood LDL-C levels have been advocated.[1–3] Therefore, the dyslipidemia guidelines in China should still recommend LDL-C as a primary interventional target.

In clinical practice, the majority of doctors frequently set LDL-C reduction target to prevent ASCVD. However, a few recent dyslipidemia guidelines published outside of China have recommended not setting LDL-C reduction target[1,2] since there has been no evidence from randomized controlled trials (RCT) to support specific LDL-C target. It is also unknown which LDL-C target leads to the most significant reduction in ASCVD risk. If a specific LDL-C target is set, overtreatment with lipid-lowering drugs might occur in patients with a particularly high baseline LDL-C level; in contrast, the treatment might be inadequate or deficient for patients with a baseline LDL-C that is low or within normal limits.

Evidently, removing the LDL-C reduction target will further cause a series of problems. First, doctors themselves will misapprehend that the aim is not to reduce LDL-C level but merely the use of certain drugs; second, patient compliance with cholesterol-lowering medication regimens will be seriously compromised. From the perspective of benefitting from lipid-lowering treatment, long-term adherence to treatment is the most significant factor. It is only by setting an LDL-C reduction target that doctors can accurately evaluate treatment effectiveness and effectively communicate with their patients, thereby improving patient compliance with lipid-lowering drug

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.cdtm.2016.04.001

regimens. Therefore, there is no evidence in support of eliminating the LDL-C reduction target in China that will get more benefits.

Non-high-density lipoprotein cholesterol (non-HDL-C) can also be used as a target in lipid-lowering therapy. However, since clinicians in China generally have low awareness of non-HDL-C, it would be inappropriate at this stage to set it as the primary target, although it could be considered a secondary target of lipid-lowering therapy. Non-HDL-C is the sum of all cholesterol contained in lipoproteins other than HDL particles, of which LDL-C accounts for more than 70%. Other constituents include chylomicrons, very low density lipoprotein, intermediate density lipoprotein, and cholesterol (a) particles in lipoprotein. Non-HDL-C may reflect the cholesterol levels of all atherosclerosis pathogenic lipoproteins and is calculated as: non-HDL-C = total cholesterol minus HDL-C.

The basic target value for blood lipids (referred to as the target value) in lipid-lowering therapy should be determined according to ASCVD risk. Since the optimal target and virulence threshold values of LDL-C (or non-HDL-C) have not been ascertained, the determination of target value in lipid-lowering therapy could differ from that of those during antihypertensive treatment and hypoglycemic therapy. The recommendation of lowering LDL-C to a certain point (the target) is mainly based on the consideration of the risk-benefit ratio: patients at higher risk of future cardiovascular events would benefit more; and reducing the LDL-C level will result in greater cardiovascular clinical benefits, but the associated adverse reactions (from drugs or otherwise) will also increase. Health economics is also an important factor when determining the target.

All patients with a clinical diagnosis of ASCVD (including acute coronary syndrome, stable coronary artery disease, post-revascularization, ischemic heart disease, ischemic stroke, transient cerebral ischemia attack, peripheral atherosclerosis, etc)[1] comprise a very-high-risk group. As for the non-ASCVD population, risk assessment requires implementation according to risk factor number and severity. The population can then be divided into high-risk, medium-risk, and low-risk groups, according to which LDL-C reduction targets are set. The LDL-C levels that trigger drug treatment and the LDL-C targets differ widely among the different risk groups.

In the Chinese Guidelines for the Treatment and Prevention of Dyslipidemia revision process, there was an intense debate on whether the recommended LDL-C reduction target for the high-risk group should be set at LDL-C < 1.8 mmol/L (70 mg/dl) or < 2.0 mmol/L (80 mg/dl). Three rounds of voting were used to make the final formal decision of the LDL-C reduction target for the very-high-risk group. The majority of the respondents advocated for a target of <2.0 mmol/L (80 mg/dl) in the first two rounds. However, in the final round, a small majority supported the target of <1.8 mmol/L (70 mg/dl). This value is consistent with the recommended target in most international lipid guidelines as well as those in other areas domestically such as in diabetes treatment. More significantly, recently published results on statins and ezetimibe combination therapy in a clinical trial[4] showed that, after a decrease in the LDL-C target from 1.8 mmol/L (69.5 mg/dl) to 1.4 mmol/L (53.7 mg/dl), the absolute risk of cardiovascular events was further reduced by 2% and the relative risk was reduced by 6.4%. However, the risk of cardiovascular or all-cause mortality did not decrease.

Clearly, the clinical evidence is insufficient for all recommended LDL-C targets. My personal opinion in favor of recommending <2.0 mmol/L (80 mg/dl) as the target is based on several reasons. First, the optimum target value of blood lipids should be in Chinese adults is unclear, and much controversy persists internationally about how to determine the target value. There are even cholesterol guidelines without recommended target values. The 2007 Chinese Guidelines for the Treatment and Prevention of Adult Dyslipidemia proposed that the LDL-C target should be <2.0 mmol/L (80 mg/dl) in the very-high-risk group,[3] which can be used as an important reference. Second, numerous studies have confirmed that reducing the LDL-C target to <2.0 mmol/L (80 mg/dl) has already proven beneficial for ASCVD or patients at high risk. (3) The clinical benefit from lipid-lowering therapy is mainly from long-term adherence to treatment. Therefore, patients' accessibility and compliance is the key to achieving benefit. Fourth, in clinical practice, although further reducing LDL-C level could slightly increase the clinical benefits for specific patients, it leads to increased individual and public healthcare costs and limits the cost-effectiveness of social healthcare. And fifth, animal lipid studies have shown that atherosclerosis generally does not occur in animals with an LDL-C < 2.0 mmol/L (80 mg/dl). Direct measurement of atherosclerotic plaques using serial intravascular ultrasonography showed that achieving a serum LDL-C < 1.9 mmol/L (75 mg/dl) could halt the progression of atherosclerosis.[5]

In addition, although many clinical trials[6–10] have demonstrated that high-dose statin therapy could further lower the LDL-C level to promote a clinical benefit, in most clinical trials, the mean LDL-C level in the intensive lipid-lowering therapy group was 1.9–2.5 mmol/L (72–95 mg/dl), indicating that even with the maximum dose of statins (i.e. atorvastatin 80 mg/d), only about half

of the group achieved a level of 2.0 mmol/L (80 ml/dl). The benefit from intensive statin therapy is related to the baseline LDL-C levels. Although all patients with a baseline LDL-C $\geq$ 1.8 mmol/L (70 mg/dl) can benefit from statin therapy, patients with a baseline LDL-C < 2.0 mmol/L (80 mg/dl) received relatively smaller benefits. More importantly, all of the results from clinical studies of intensive statin therapy show that a manifold increase in statins could reduce the ASCVD incidence to a statistically significant level; but the absolute benefit level was minor and all-cause mortality had not decreased as well.[11] These findings suggest that although further reductions in LDL-C levels will offer potential clinical benefit, the absolute margin of benefit is smaller. Recommendations in the guideline were proposed from the perspective of the overall population, which considers the majority of patients with ASCVD. Therefore, it should be very reasonable to recommend LDL-C < 2.0 mmol/L (80 mg/dl) as the basic target. Of course, depending on the clinical condition of particular patients, if adverse drug reactions can be avoided and personal expense is not an issue, the LDL-C level could be reduced to a lower level.

In clinical practice, baseline LDL-C levels can reach high or low extremes. In these cases, the treatment strategy based on LDL-C target values should be modified. For both cases, the LDL-C percentage reduction strategy is feasible. Based on existing lipid-lowering clinical trials, the majority of results from those clinical studies suggested that lowering LDL-C levels by 30−40% can produce a clinical benefit. Since it is difficult for patients with higher baseline LDL-C levels to achieve the target value using existing drugs, the levels should be reduced by at least 40%. Certain very-high-risk patients have a baseline LDL-C level that is within the target range; thus, a reduction of approximately 30% can be considered.

References

1. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013ACC/AHA-Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *JACC*. 2014;63:2889−2934.
2. Rabar S, Harker M, Flynn N, Wierzbicki AS, On behalf of the Guideline Development Group. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *BMJ*. 2014;349:1−6.
3. Expert Panel of Chinese Guidelines for the Treatment and Prevention of Dyslipidemia. Chinese guidelines for the treatment and prevention of dyslipidemia. *Chin J Cardiol*. 2007;35:390−410.
4. Cannon CP, Blazing MA, Giugliano RP, et al, IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015 18;372:2387−2397.
5. Williams KJ, Feig JE, Fisher EA. Rapid regression of atherosclerosis: insights from the clinical and experimental literature. *Nat Clin Pract Cardiovasc Med*. 2008;5:91−102.
6. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease atorvastatin versus revascularization treatment investigator. *N Engl J Med*. 1999;341:70−76.
7. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495−1504.
8. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. *JAMA*. 2004;292:1307−1316.
9. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatinin patients with stable coronary disease. *N Eng J Med*. 2005;352:1425−1435.
10. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. The IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437−2445.
11. Giraldez RR, Giugliano RP, Mohanavelu S, et al. Baseline low density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT−TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy−Thrombolysis in Myocardial Infarction 22) analysis. *J Am Coll Cardiol*. 2008;52:914−920.

Edited by Wei-Zhu Liu