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Perspective

Clinical considerations of lipid target and goal in dyslipidemia control

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In clinical practice, physicians often use certain strategies based on guidelines or recommendations from experts. This is because in the era of evidence-based medicine, clinicians are more willing to make "evidence-based" decisions. This is also the case in the field of lipid-lowering therapy. The term "lipid-lowering therapy" does not simply refer to items with abnormal values in the lipid profile, and individualized management is all the more important in the overall assessment of a patient. Thus, it is easy to conclude that doctors need a relatively authoritative assessment system to determine whether a patient requires lipid-lowering therapy, as well as the intensity of therapy, the blood lipid indicators for therapy, and the expected target of therapy. The above-mentioned issues are briefly reviewed in this paper.

Definitions of "target" and "target goal" in lipid management

Clinical routine lipid screening includes screening for total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Such indicators provide essential information on the lipid profile for the prevention and treatment of cardiovascular diseases.

Gradual progress in the study of the relationship between cholesterol and cardiovascular disease (CVD) and the gradual accumulation of clinical evidence have enabled a better understanding of the importance of all lipid components in the pathogenesis of CVD, and the concepts of "target" and "target goal" have been generated. Therefore, in recent years, LDL-C and non-HDL cholesterol (non-HDL-C) have been identified as the "targets" in the guidelines for lipid management, and apolipoprotein B (ApoB) is the secondary target in some guidelines.[1–3]

For the corresponding targets, different "target goals" are defined in most guidelines according to the levels of risk, to guide the lipid management in different groups and to minimize the risk of cardiovascular events on a scientific basis.

Recommendations for the stratification of "target" and "target goal" in international and domestic lipid guidelines

In 1988 and 1993, when the US National Cholesterol Education Program (NCEP) Adult Treatment Panel I (ATP I) was developed and the ATP II was updated, the evidence-based clinical information for lipid management, especially for the use of statin drugs in cholesterol-lowering therapy, was not sufficient.[4,5] At that time, the harmful effect of hypercholesterolemia on cardiovascular

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prognosis had been recognized, and both ATP I and ATP II recommended the use of LDL-C as the primary target for intervention. The development and updates of the guidelines were mostly based on epidemiological evidence or the evidence from statin studies. The risk stratification of target populations for lipid management was emphasized in the European lipid management guidelines (hereinafter referred to as "European guideline")[1] jointly issued for the first time by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) in 2011, and in the patient-centered management of dyslipidemia released by the National Lipid Association (NLA) in 2014 (hereinafter referred as "the latest US recommendation"). Additionally, very high, high, moderate, and low atherosclerotic risk were stratified.[3] Among various guidelines, there are some differences in the definitions of the above-mentioned risk stratifications. Among these, the representative European guideline proposed the SCORE rating scale. In the 2013 US lipid guideline, an expert team developed assessment tools for adult cardiovascular disease risk, in order to conduct quantitative assessment in patients.[2] The expert team developed a new cardiovascular risk scoring system using a large number of research data based on different ethnic backgrounds and in different areas, including the Framingham Heart Study (FHS), the Atherosclerosis Risk in Community Study (ARIC), the Coronary Artery Risk Development in Young Adults Study (CARDIA), and the Cardiovascular Health Study (CHS). The risk assessment equation can predict the risks of CVD and stroke.

Compared with the NCEP ATP III and the 2007 Chinese lipid guidelines,[6,7] the European guideline has a broader definition of very high-risk groups, and LDL-C treatment target is more stringent. In NCEP ATP III, a very high-risk population includes patients with a combination of risk factors of coronary heart disease and acute coronary syndrome (ACS), and the recommended goal for lipid lowering is <1.8 mmol/L (70 mg/dl) or a reduction of ≥40%. According to the Chinese guidelines, only ACS patients and those with a combination of ischemic CVD and diabetes belong to the very high-risk population, and the recommended goal for lipid lowering is <2.0 mmol/L (80 mg/dl) or a reduction of ≥40%. On the other hand, in the European guidelines, a very high-risk group is defined as the population with a SCORE value of >10%, or patients diagnosed with CVD, type 2 diabetes mellitus (T2DM), or type 1 diabetes mellitus (T1DM), in combination with target organ damage and moderate to severe chronic kidney disease (CKD). The LDL-C goal for a very high-risk patient is <1.8 mmol/L (70 mg/dl) or a reduction of ≥50%. The LDL-C levels required by European guidelines for high-risk patients with a significantly high level of individual risk factors (5% ≤ SCORE < 10%) and moderate-risk patients (1% ≤ SCORE < 5%) were <2.6 mmol/L (100 mg/dl) and <3.0 mmol/L (115 mg/dl), respectively. This recommended LDL-C level is more active than that in NCEP ATP III<3.4 mmol/L (130 mg/dl) and Chinese guidelines (<3.2 mmol/L (120 mg/dl)). The latest US guidelines causing widespread controversy proposed abandoning the target value because currently no evidence from randomized controlled clinical trials supports reducing the lipid level to the above-mentioned target value in clinical practice. As a result, the latest US guideline no longer includes the LDL-C and non-HDL-C target values in the primary and secondary prevention of coronary heart disease. However, this guideline has stressed that for patients with atherosclerotic cardiovascular disease (ASCVD), regardless of baseline LDL-C levels, patients <75 years old should start high-intensity statin therapy, and high-intensity, moderate and low statin therapies are defined according to the magnitude of LDL-C reduction. High-intensity statin therapy is defined as the daily dose that can reduce LDL-C level by ≥50%. The latest US recommendation indicates that the major risk factors for ASCVD include: (1) age (men ≥45 years, women ≥55 years old); (2) a family history of premature coronary heart disease (male first-degree relatives <55 years, female first-degree relatives <65 years); (3) smoking; (4) high blood pressure; (5) low HDL-C level (male ≤40 mg/dl, female ≤50 mg/dl); (6) elevated levels of non-HDL-C and LDL-C; and (7) diabetes. High-risk and very high-risk groups include patients with (1) ASCVD; (2) LDL-C ≥190 mg/dl; (3) T1DM or T2DM; and (4) stage 3 or higher CKD. This lipid management recommendation combines different views on whether to retain the LDL-C target values in these guidelines, and finally provides explicit recommendation on retaining the LDL-C target value. The identified LDL-C target values according to the risk stratification are the same as those in the European guideline.

Compared with the NCEP ATP III as well as the Chinese guideline,[6,7] the European guideline continues to affirm statins as the cornerstone in the treatment of atherosclerosis, and more actively recommends starting drug treatment for high-risk and very high-risk groups. In NCEP ATP III and the 2007 Chinese guidelines on prevention and treatment of dyslipidemia in adults drug therapy will be initiated for high-risk (coronary heart disease, stroke, diabetes, ACS) patients with an LDL-C level of >2.6 mmol/L (100 mg/dl), and may be considered with an LDL-C level of <2.6 mmol/L (100 mg/dl). The European guideline

recommends starting drug therapy immediately for very high-risk (coronary heart disease, stroke, diabetes) patients with an LDL-C level of >1.8 mmol/L (70 mg/dl), and may also be considered even if the LDL-C level is <1.8 mmol/L (70 mg/dl). For ACS and myocardial infarction (MI) (including acute myocardial infarction and previous myocardial infarction) patients, statin therapy should be immediately started regardless of LDL-C levels. For the first time, the European guideline has proposed that CKD patients are an very high-risk group for cardiovascular disease. Lowering LDL-C level may reduce the risk of CVD in patients with CKD, and therefore should be recommended (IIa/B). Statins are recommended to moderately delay the progress of renal dysfunction, thus preventing the development of end-stage renal disease requiring dialysis treatment (IIa/C). Given the benefits of statins on pathologic proteinuria (>300 mg/dl), the use of statins should be considered for stage 2–4 CKD patients (IIa/B). For patients with moderate to severe CKD, the use of a statin alone or in combination with other drugs should reduce the LDL-C level to <1.8 mmol/L (70 mg/dl) (IIa/C), and statins that are metabolized via the liver are preferred.

The review of evidence in the new US guideline focuses on the cholesterol management that has the greatest significance in lipid lowering, and suggests the type of patients who should accept "statin" treatment, and the intensity of statin therapy that can achieve the precise benefit of reducing ASCVD risk. At the same time, the new guideline uses the evidence from a randomized clinical trial study as its basis, and proposes four groups that can benefit from statins: (1) ASCVD patients with clinical evidence; (2) patients with primary elevation of LDL-C ≥190 mg/dl (4.9 mmol/L); (3) diabetic patients aged 40–75 years with no clinical evidence of ASCVD and an LDL-C level of 70–189 mg/dl (1.8–4.9 mmol/L); and (4) patients with no clinical evidence of ASCVD, or diabetic patients who are 40–75 years old, with an LDL-C level of 70–189 mg/dl (1.8–4.9 mmol/L) and a 10-year ASCVD risk of ≥7.5%.If a patient with ASCVD does not have contraindications or statin-related adverse events, he/she should receive high-intensity statin therapy, including rosuvastatin (the recommended dose: 20–40 mg) or atorvastatin (the recommended dose: 80 mg), to reduce the LDL-C level by at least 50%. For the patients with dose-related adverse reactions, the treatment can be changed to moderate-intensity statin therapy. The patients with an LDL-C level of ≥190 mg/dl should receive high-intensity statin treatment, to reduce the level of LDL-C by at least 50%. The diabetic patients aged 40–75 years with no clinical ASCVD should receive at least moderate-intensity statin therapy, to reduce the level of LDL-C by 30%–40%; Patients who are 40–75 years of age with no clinical ASCVD or with diabetes and an LDL-C level in the range of 70–189 mg/dl and a 10-year ASCVD risk of >7.5% should receive moderate or high-intensity statin treatment.[8]

Clinical considerations of "target" and "target goal" in lipid management

In the 2013American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol, the recommended target goal was abandoned, which caused hesitation and confusion among domestic and international medical staff. The vague, recommended strategy for "target" and specific "target goal" had some negative effects. The 2014 NLA recommendations for dyslipidemia management retained the target goal based on an explicit determination of "target," clearly reflecting the important clinical significance of defining "target" and "target goal" in lipid-lowering therapy. The ultimate goal of developing guidelines is to regulate medical practice. Therefore, a guideline must be closely combined with clinical practice in order to properly promote and apply the guidelines. In clinical practice, when advising specific patients to follow medical recommendations, clinicians can use a patient-centered approach by performing risk stratification based on the latest recommendations for the management of dyslipidemia. LDL-C should be used as the primary target, the required target value for LDL-C is determined, and both doctors and patients should have a well-defined target and goal. Doctors can choose appropriate and reasonable lipid-lowering treatments, and with the "lipid-lowering target," patients can improve their therapeutic compliance and level of cooperation, thereby reducing the discontinuation of lipid-lowering drugs due to unclear goals. As a result, the benefits for patients with different risk levels after stratification can be maximized for lipid-lowering treatment, and the occurrence and development of cardiovascular events can be minimized.

Of course, it is worth noting that clinical situations are complex, although one may understand the clinical significance of "target" and "target goal" in lipid-lowering therapy. In specific clinical practice, one may encounter specific issues. For example, should lipid-lowering therapy be continued when the patient's

LDL-C has already reached the target? Should non-statin drugs be combined when the existing intensive statin therapy cannot reduce the patient's LDL-C to the target? How to deal with patients' concerns about "excessive lowering of LDL-C level?" In the 2013 ACC/AHA guidelines on the treatment of blood cholesterol, the reason to abandon the target value is that a large-scale RCT cannot determine "the threshold value of LDL-C level at which there is no reduction in cardiovascular events." There are potential positive effects on clinical practice from "abandoning the target." For example, doctors and patients will not easily adjust the dose of statins based on blood lipid tests; the dose of statins will not easily be reduced for patients whose LDL-C level reaches the target; and non-statin drugs with no confirmed clinical benefits will not easily be combined for patients whose LDL-C level does not reach the target.[9]

Therefore, when determining the retention of "target" and "target goal" in lipid-lowering therapy, one should correctly apply the basic concepts of "target" and "target goal," to better apply the "guideline recommendation" in clinical practice.

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