Obstacles to Optimal Lipid-Lowering Therapy — Any Solution? —

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In association with the epidemic of abdominal obesity and type 2 diabetes mellitus, it has been projected that atherosclerotic cardiovascular disease (ASCVD) will become a leading cause of death worldwide, which suggests the need to adopt an efficacious preventive approach for improving cardiovascular outcomes. Current therapeutic guidelines recommend lowering low-density lipoprotein cholesterol (LDL-C) levels with a statin in subjects who exhibit an elevated risk for ASCVD.^{1,2} This is based on accumulating evidence from numerous large-scale clinical trials that have consistently demonstrated favorable effects of statin therapy on atherosclerotic cardiovascular outcomes.^{3,4} As well, serial intravascular imaging studies have

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shown that lowering the LDL-C level with statins slows disease progression.⁵ Furthermore, achieving a very low LDL-C level with high-intensity statin therapy induced regression of coronary atheroma.⁶ Accordingly, the statin regimen for stricter control of LDL-C has become a cornerstone of treatment in both the primary and secondary prevention settings.

Despite statin-mediated favorable effects, recent studies have highlighted the need to cope with several issues of lipid-lowering therapy for optimal management. In this

Light blue: LDL-C, Orange: HDL-C, Gray: TG, Yellow: Non-HDL-C, Blue: All

Figure. Frequency of achieving lipid goals. HDL-C, high-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; TG, triglycerides. (Cited with permission from Tada H, et al.¹⁰)

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issue of the Journal, Nagar et al⁷ reported the frequency of continuing statin use and its intolerance, and their cardiovascular outcomes in patients with ASCVD and type 2 diabetes mellitus, respectively, from the Japan Medical Data Center database. One of striking observation is that almost one-third of each cohort discontinued statin therapy within 12 months of its commencement. Discontinuation of a statin is reportedly associated with an increased risk for cardiovascular event,⁸ suggesting the importance of statin adherence to optimally reduce risk of future cardiovascular events. The current observation in this study underscores the need to enhance physicians' and patients' awareness of the importance of the preventive effects of statin therapy.

Statin-related side effects are a major obstacle to treatment continuation. Musculoskeletal complaints and increases in creatine kinase and/or alanine aminotransferase do not occur frequently under statin therapy, but statin intolerance requires physicians to decrease the dose, discontinue or switch to a non-statin lipid-lowering drug. In this study, potential statin intolerance was observed in 10.0% and 8.4% of the ASCVD and type 2 diabetic cohorts, respectively.⁷ This finding highlights the need to establish an applicable and effective approach to achieving optimal control of lipid targets. Nissen et al⁹ recently investigated the occurrence of muscle-related statin intolerance in a double-blind, placebo-controlled crossover procedure to re-challenge with atorvastatin in the GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3) trial. In their study, which enrolled patients with a strong history of muscle-related statin intolerance, the discontinuation rate with atorvastatin was 42.6%. Furthermore, 26.5% of subjects reported similar symptoms with placebo but not atorvastatin, demonstrating that reported muscle symptoms are not always related to statin use.⁹ This study suggests that appropriate and correct evaluation of statin intolerance is required to optimally manage patients at high risk for ASCVD.⁹

Although achieving a lower LDL-C level with high-intensity statin treatment is recommended, the frequency of subjects under optimal LDL-C control is not satisfactory. A recent study reported that the proportion of subjects who achieved the guideline-recommended LDL-C goal was relatively low (Figure),¹⁰ which indicates the need to further intensify lipid-lowering therapy. In the current study, however, only 11.2% and 10.6% of patients in the 2 cohorts received further intensified lipid-lowering therapy despite their high-risk cardiovascular backgrounds.⁷ Given that undertreatment of LDL-C levels leads to suboptimal control, disease progression and more frequent cardiovascular events, more efforts are needed to adopt the guideline-based lipid-lowering approach for optimization of patients' outcomes.

Ezetimibe has become an additional non-statin agent used to lower LDL-C levels by 15–20%. Its antiatherosclerotic effects have been shown by a recent clinical trial and an intravascular ultrasound study.^{11,12} In both of those studies, combination use of a statin and ezetimibe was associated with achieving a lower LDL-C level, more regression of coronary atherosclerosis and a significant reduction of ASCVD in patients with coronary artery disease. Another class of additive lipid-lowering drugs is the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which have been shown to lower LDL-C levels by approximately 60%. The FOURIER¹³ and GLAGOV¹⁴ studies have demonstrated better cardiovascular outcomes

and regression of coronary atherosclerosis under evolocumab use. In addition, the GAUSS 3 trial showed treatment efficacy even in patients with statin intolerance. These 2 therapeutic approaches will play more important roles in the secondary prevention settings.

Although a PCSK9 inhibitor is a quite efficacious agent with regard to lowering LDL-C levels and reducing the cardiovascular event risk, cost-effectiveness should be also considered. One recent analysis reported that the use of PCSK9 inhibitors may substantially increase healthcare costs.¹⁵ This indicates the need to establish efficacious as well as cost-effective preventive approaches to improving cardiovascular outcomes. Recently, therapies that modulate residual risks after statin therapy have received much attention with regard to efficacy. Modifying high-density lipoprotein, triglyceride-rich lipoproteins and other atherogenic lipid targets could become additional therapies to prevent future events. Future investigation will elucidate better preventive management with regard to both efficacy and cost-effectiveness.

Conflict of Interests

None.

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