



Optimal Low-Density Lipoprotein Cholesterol Level for Primary Prevention in Koreans with Type 2 Diabetes Mellitus

Ji Yoon Kim, Nam Hoon Kim


Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea

Diabetes mellitus (DM) is one of the most important risk factors for cardiovascular disease (CVD) [1], requiring intensive strategies for cardiovascular risk management in affected patients. A linear relationship between low-density lipoprotein cholesterol (LDL-C) level and incident CVD has been observed in patients with DM, as well as in individuals without DM [2,3]. Lowering LDL-C levels with statin therapy is currently a mainstay of dyslipidemia management in people with DM [4-8]. Previous randomized controlled trials of statins such as the Collaborative Atorvastatin Diabetes Study (CARDS) have shown that use of statins reduced the risk of adverse cardiovascular events in patients with type 2 diabetes mellitus (T2DM) [9]. In the 2013 American College of Cardiology/American Heart Association guidelines, individuals with DM aged 40 to 75 years are included in four statin benefit groups, in which the cardiovascular benefits of statins clearly exceed the possible harms [10].

However, the level to which LDL-C should be lowered remains controversial, largely due to the limited number of treat-to-target trials for statin and nonstatin therapies. Nonetheless, the concept of “the lower, the better” for LDL-C level is widely accepted based on clinical trials of high-intensity statins [11,12], ezetimibe [13], and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors [14,15]. These trials demonstrated that an LDL-C level less than 70 mg/dL was achievable with intensive management, resulting in a lower incidence of adverse cardiovascular events than that with higher levels of

LDL-C using low- to moderate-intensity statins. Accordingly, the 2023 American Diabetes Association guideline recommends using high-intensity statins to reduce LDL-C levels by $\geq 50\%$ of the baseline and to < 70 mg/dL in patients with DM aged 40 to 75 years at high cardiovascular risk [4]. Similarly, the 2021 European Society of Cardiology recommends LDL-C level less than 70 mg/dL for patients with T2DM [5]. However, there is little evidence whether the same LDL-C target could be applied to Asians or Koreans. Most randomized controlled trials of statin or nonstatin therapies included a small number and proportion of Asians. In addition, some differences in the response to statin therapy have been observed between Europeans and Asians [16,17].

In this issue of *Diabetes & Metabolism Journal*, Moon et al. [18] provided important evidence of appropriate LDL-C level for cardiovascular health in Korean patients with T2DM. This study evaluated the incidence of CVD according to LDL-C level, type of comorbidity, and number of cardiovascular risk factors in patients with T2DM. This retrospective cohort study was conducted using the Korean National Health Insurance Service database and included 248,002 patients with T2DM without CVD. As a result, the risk of incident CVD increased linearly from an LDL-C level ≥ 70 mg/dL in most patients with T2DM, regardless of the type of comorbidities. The appropriate target LDL-C level could be considered < 70 mg/dL when comorbidities are present and < 100 mg/dL when the duration of DM is less than 5 years or if hypertension is absent. If pa-

Corresponding author: Nam Hoon Kim  <https://orcid.org/0000-0002-9926-1344>
Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, 73 Incheon-ro, Seongbuk-gu, Seoul 02841, Korea
E-mail: pourlife@korea.ac.kr

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tients have three or more cardiovascular risk factors, the target LDL-C level could be less than 55 mg/dL.

Nevertheless, as the authors discussed in their manuscript, the question remains whether this type of cohort study can provide a 'target' LDL-C level for cardiovascular risk reduction. LDL-C levels in this analysis were measured once in 2009, when the statin prescription rate was only 35.9% in patients with T2DM. The primary outcome was measured until 2018, but the changes in LDL-C levels and a new statin prescription during the follow-up period were not included. Considering the continuous increase in statin prescription rate over the past 10 years [19], the LDL-C levels among patients have probably decreased and the gaps between the individuals narrowed. In the context of a retrospective study, adjustments for the clinicians' judgment regarding the prescription of lipid-lowering drugs could not be made. Therefore, an analysis focusing on statin users (Supplementary Table 2 in [18]) has great significance. The LDL-C level of statin users can be interpreted as the achieved LDL-C level, which more clearly presents the target LDL-C level. As a result, the appropriate level of LDL-C in statin users was considered to be <70 mg/dL, consistent with the primary analysis. Of note, adverse cardiovascular events occurred less frequently in statin users than in non-users even though they had the same LDL-C level, supporting the pleiotropic effects of statins beyond LDL-C lowering [20].

In individuals younger than 40 years, the risk of adverse cardiovascular events significantly increased only when the LDL-C level was greater than 190 mg/dL, suggesting a smaller effect of the LDL-C level on the development of CVD in younger patients than in older patients. However, as discussed by the authors, this may be due to the small number of cardiovascular events in this age group. Considering that the hazard ratios of primary outcomes in younger patients with higher LDL-C level were greater than those in older age groups, a larger-scale study may reveal a significant association between LDL-C level and development of CVD in younger patients with T2DM.

The conclusions of this study are as follows. For most patients with T2DM and comorbidities, the appropriate target LDL-C level can be less than 70 mg/dL. For patients without additional cardiovascular risk factors or those aged <40 or >75 years, the target LDL-C level could be less stringent. Considering that most clinical trials of lipid-lowering drugs included patients with established CVD [11-15], there was not sufficient data on optimal LDL-C level for primary prevention in people at risk of CVD. It is noteworthy that this study pro-

vides evidence for appropriate LDL-C levels for the primary prevention of CVD in Korean patients with T2DM.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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