Should Measures of High-Density Lipoprotein Function Be Added to the Low-Density Lipoprotein Cholesterol Target Level-Based Guidelines for Prevention of Atherosclerotic Disease?

Ichiro Sakuma, MD, PhD; Katsunori Ikewaki, MD, PhD

The pivotal role of low-density lipoprotein cholesterol (LDL-C) in prevention of atherosclerotic cardiovascular disease (ASCVD) is well established.\(^1,2\) However, residual risk after lowering LDL-C and the importance of cardiometabolic factors, including glucose tolerance, have been recently recognized.\(^3,4\) Along these lines, as one of the cardiometabolic factors, the role of high-density lipoprotein cholesterol (HDL-C) in ASCVD prevention is still controversial.\(^1,2\)

For example, a very recent Japanese mega-trial comparing the effects of high-dose (4 mg/day) and low-dose (1 mg/day) pitavastatin therapy on the secondary prevention of ASCVD in 13,054 patients with stable coronary artery disease (REAL-CAD) reported that, with a median 3.9-year follow-up period, high-dose treatment (LDL-C reduced to 76.6 mg/dL) as compared with low-dose (LDL-C reduced to 91.0 mg/dL) significantly reduced the number of ASCVD events.\(^5\) In this trial, a subanalysis based on HDL-C would provide evidence for a potential role of HDL on ASCVD prevention.

However, clinical trials that aimed to investigate the anti-atherosclerotic effects of increased HDL-C levels using drugs such as nicotinic acid and cholesterol ester transferase protein (CETP) inhibitors failed to demonstrate a reduction in the risk of ASCVD events,\(^4\) except in the REVEAL study using anacetrapib.\(^6\) Therefore, a novel hypothesis that HDL function, but not the HDL-C level, would be a clinically relevant marker and a therapeutic target for ASCVD has been proposed.\(^7,8\)

### Table. LDL-C Target Levels for Prevention of Atherosclerotic Disease in Each Society Guidelines

<table>
<thead>
<tr>
<th>Secondary prevention</th>
<th>ACC/AHA 2013(^10)</th>
<th>EAS/ESC 2016(^12)</th>
<th>Korean 2015(^13)</th>
<th>Japanese 2017(^14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS, IHD, cerebrovascular accident, PAD</td>
<td>LDL-C &lt;50% ↓</td>
<td>LDL-C &lt;70 mg/dL (1.8 mmol/L)</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
</tr>
<tr>
<td>DM with Cx</td>
<td>LDL-C &lt;50% ↓</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
</tr>
<tr>
<td>CAD equivalent</td>
<td>LDL-C &lt;50% ↓</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;100 mg/dL</td>
</tr>
<tr>
<td>DM without Cx, carotid artery disease, abdominal aneurysm</td>
<td>LDL-C &lt;50% ↓</td>
<td>LDL-C &lt;70 mg/dL</td>
<td>LDL-C &lt;100 mg/dL</td>
<td>LDL-C &lt;100 mg/dL</td>
</tr>
</tbody>
</table>

| Primary prevention | | | | |
|-------------------|----------------|----------------|------------------|
| Intermediate risk (≥2 risk factors) | LDL-C <50% ↓ | LDL-C <70 mg/dL | LDL-C <130 mg/dL | LDL-C <120 mg/dL |
| "Low risk (≤1 risk factor) DM without Cx+with Cx | LDL-C <70 mg/dL | LDL-C <160 mg/dL | LDL-C <160 mg/dL |
| HDL-C Not mentioned | HDL-C ≥40 mg/dL | HDL-C ≥40 mg/dL | HDL-C ≥40 mg/dL |
| HDL function Not mentioned | HDL function Mentioned | HDL function Not mentioned | HDL function Mentioned |

ACS, acute coronary syndrome; CAD, coronary artery disease; Cx, complication; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol; IHD, ischemic heart disease; LDL-C, low-density lipoprotein-cholesterol; PAD, peripheral artery disease.

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Rader, who firstly proposed the HDL function hypothesis, and his colleagues have reported that the capacity of HDL to efflux cholesterol from macrophages (i.e., cholesterol efflux (CE)) is an independent and negative predictor for coronary artery disease.\(^5\) Ikekawa and colleagues then extended this finding to a Japanese population.\(^9\) Further, Koba and Ikekawa showed that rehabilitation after acute coronary syndrome significantly improved HDL CE capacity.\(^2\) These results should be interpreted with caution, because these studies were cross-sectional; however, 2 later cohort studies independently demonstrated that CE capacity was a negative risk factor for ASCVD.\(^{10,11}\)

In this issue of the Journal, Jung et al report that in diabetic patients with dyslipidemia rosuvastatin 20 mg treatment increased HDL function as assessed by CE capacity, improved vascular endothelial function (flow-mediated dilatation (FMD) of the brachial artery), reduced carotid intima-media thickness (cIMT), and favorably changed biomarkers related to lipid metabolism and atherosclerosis.\(^\text{12}\) Favorable effects of intensive statin treatment on HDL function to ameliorate CE capacity in addition to lipid-related biomarkers have already been acknowledged,\(^\text{13}\) even in diabetic patients.\(^\text{14}\) Thus, the novel findings of the study by Jung et al are largely confined to the relationship between increased CE capacity and changes in FMD and cIMT.

What is amazing in the results of Jung et al\(^\text{12}\) is that with only 12-week treatment with 20 mg rosuvastatin to diabetic patients (mean age: 50±11 years) cIMT at both side bulbs and the internal carotid area decreased significantly by 0.04 to 0.11 mm. A similar research investigating the effects of rosuvastatin treatment (mean: 7.7 mg) to Asian patients with thickened cIMT (mean age: 64±8 years) for as long 1 year\(^\text{15}\) and even 2 years\(^\text{16}\) failed to demonstrate a significant decrease in cIMT, although this research could show that a decrease in mean cIMT is significantly related to the attained LDL-C level.\(^\text{17}\) Thus, further studies enrolling more diabetic subjects and having a longer duration are warranted to reproduce the present findings on cIMT, and to confirm the mechanisms of how CE capacity was ameliorated and how increased CE capacity and changes in FMD and cIMT were positively correlated.

The report by Jung et al\(^\text{12}\) raises the important notion of whether HDL function, including CE capacity and HDL particle size or number, should be added to the guidelines or recommendations for treatment of dyslipidemia for prevention of atherosclerotic diseases, especially in patients with diabetes. The present guidelines in the world\(^{1,2,14,19}\) are mainly LDL-C targeted and only the European guideline refers to HDL function (Table). It is eagerly hoped that a description of HDL functions will be added to the guidelines for prevention of atherosclerotic diseases in many countries when the roles of HDL function are settled after further investigations and clinical research concerning this factor.

**COI Disclosures**

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**References**


