

Editorial



The Long and Winding Road: To the Proper Understanding of High-density Lipoprotein

Jidong Sung , MD, MPH, PhD

Division of Cardiology, Department of Medicine, Prevention & Rehabilitation Center, Heart Vascular & Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

OPEN ACCESS

Received: Jan 12, 2020

Accepted: Jan 15, 2020

Correspondence to

Jidong Sung, MD, MPH, PhD

Division of Cardiology, Department of Medicine, Prevention & Rehabilitation Center, Heart Vascular & Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea.

E-mail: jdsung@skku.edu

Copyright © 2020. The Korean Society of Cardiology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Jidong Sung 

<https://orcid.org/0000-0002-1006-5727>

Conflict of Interest

The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

► See the article “Novel Associations between Related Proteins and Cellular Effects of High-Density Lipoprotein” in volume 50 on page 236.

High-density lipoprotein (HDL) is the particle transporting cholesterol from peripheral tissues to liver and thus high-density lipoprotein-cholesterol (HDL-C) has been considered as a major negative risk factor for coronary heart disease.¹⁾ In Framingham study, 12 years of follow-up showed a significant HDL-C effect on total and cardiovascular (CV) mortality.²⁾ Not only epidemiologic studies but also clinical trials such as the Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT) suggested the beneficial effect of raising HDL-C.³⁾ Not only the direct effect, the role of HDL-C as a modifying factor of statin effect has been also reported.⁴⁾ However, further studies has shown that the relationship between HDL-C and CV diseases is not that simple. Cholesteryl ester transfer protein (CETP) inhibitor is a powerful raiser of HDL-C. Several CETP inhibitors have underwent clinical trials and mostly showed negative results regarding CV risk reduction except Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) study. Even this result has met critique that it may be due to the reduction of non-HDL-C, not the increase in HDL-C.⁵⁾ A meta-analysis showed that simply increasing the amount of HDL-C does not reduce the CV risk once adjusted to low-density lipoprotein cholesterol reduction.⁶⁾ If HDL-C reduction is an inadequate solution, where do we go from here? The function of HDL particle is probably the next subject to dig into.

Khara et al.⁷⁾ reported that HDL function, measured by cholesterol efflux capacity from macrophages, had strong inverse association with both carotid intima-media thickness and the likelihood of angiographic coronary artery disease, independently of the HDL-C level. If the HDL function really influences clinical outcome, what should be done to make it clinically applicable? Probably we need a reliable biomarker for HDL function, which is standardized, accurate and easy to measure. And treatment target should be changed from simply increasing the HDL-C level to improving the HDL function. There are several ongoing (and stopped) projects to enhance reverse cholesterol transport function of HDL,⁸⁾ but the hurdle to success seems to be quite high.

In the current issue of the *Korean Circulation Journal*, Choi et al.⁹⁾ investigates the relationship between HDL functions and HDL-associated proteins. The authors used not only cholesterol efflux capacity but also endothelial nitric oxide production and vascular cell adhesion molecule expression as indices of HDL function. They reported 19 proteins were associated

with the higher HDL function and seven proteins with the lower function. While the authors are rather prudent in suggesting its clinical implications, this work seems to provide an intriguing starting point for further research. As the authors commented, there are significant limitations that clinical settings of the patients were not adequately addressed in the analysis and we do not know how the heterogeneity of subjects influenced the results. Some of the proteins they reported might be merely 'associated' and not with a significant functional role. However, at least this study may provide a candidate list for biomarker for HDL function, or even better, a list of possible target molecules for treatment to enhance HDL function. We still suffer from inadequate knowledge for HDL and is looking forward to a breakthrough. A long and winding road is ahead of us.

REFERENCES

1. Cho H. High density lipoprotein cholesterol comes of age. *Korean Circ J* 2007;37:187-90.
[CROSSREF](#)
2. Wilson PW, Abbott RD, Castelli WP. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis* 1988;8:737-41.
[PUBMED](#) | [CROSSREF](#)
3. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410-8.
[PUBMED](#) | [CROSSREF](#)
4. Kim KH, Kim CH, Jeong MH, et al. Differential benefit of statin in secondary prevention of acute myocardial infarction according to the level of triglyceride and high density lipoprotein cholesterol. *Korean Circ J* 2016;46:324-34.
[PUBMED](#) | [CROSSREF](#)
5. Kim BJ. What do we get from recent statin and CETP inhibitors trials? *J Lipid Atheroscler* 2018;7:12-20.
[CROSSREF](#)
6. Briel M, Ferreira-Gonzalez I, You JJ, et al. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ* 2009;338:b92.
[PUBMED](#) | [CROSSREF](#)
7. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011;364:127-35.
[PUBMED](#) | [CROSSREF](#)
8. März W, Kleber ME, Scharnagl H, et al. HDL cholesterol: reappraisal of its clinical relevance. *Clin Res Cardiol* 2017;106:663-75.
[PUBMED](#) | [CROSSREF](#)
9. Choi S, Park YE, Cheon EJ, et al. Novel associations between related proteins and cellular effects of high-density lipoprotein. *Korean Circ J* 2020;50:236-47.
[PUBMED](#) | [CROSSREF](#)