INCREASING HDL-C LEVELS FOR CARDIOVASCULAR BENEFIT: THE END OF A DREAM?

Angela Pirillo[1,2], Alberico Luigi Catapano[2,3]

[1]Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy

[2]IRCCS MultiMedica, Sesto S. Giovanni, Milan, Italy

[3]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

Corresponding Author:

Prof. Alberico L. Catapano

Department of Pharmacological and Biomolecular Sciences, University of Milan and IRCCS Multimedica

Via Balzaretti, 9 - 20133 Milan, ITALY

Phone number: +39250318302

Fax number: +39250318386

e-mail: alberico.catapano@unimi.it

For many decades, epidemiological studies have supported an inverse relationship between HDL-C levels and the risk of cardiovascular disease[1]. This led to focus the efforts not only in the development of lipid-lowering drugs (first of all statins), but also to the development of drugs able to increase HDL-C levels[2]. Among these drugs, fibrates, niacin and CETP inhibitors have played a major role. Despite the observations arising from epidemiological studies, interventional trials with HDL-C-raising drugs have generally failed to demonstrate a beneficial effect on cardiovascular outcomes. Mendelian randomization studies have shown that genetic variants associated exclusively with higher HDL-C levels do not associate with a decreased risk for MI[3]. Further, an U-shaped relationship exists between HDL-C levels and cardiovascular mortality, where extremely low and extremely high HDL-C levels are associated with higher cardiovascular mortality[4]. All these observations provide a challenge to the rationale for pharmacological interventions aimed at increasing HDL-C levels to reduce cardiovascular risk.

In their study, Riaz and colleagues[5] performed a large meta-analysis to evaluate the impact of HDL-C-raising pharmacological interventions on the risk of cardiovascular outcomes. They used data from 31 randomized controlled clinical trials using fibrates, niacin and CETP inhibitors in more than 150,000 patients. Looking at the lipid profile, fibrates and niacin greatly reduced TG levels, whereas HDL-C were only marginally increased (3.30 and 7.65 mg/dL, respectively); CETPi greatly induced HDL-C levels (56.30 mg/dL), and all these drugs similarly reduced LDL-C levels (~10 mg/dL). Overall, cardiovascular mortality was not affected by treatment with these drugs (RR 0.94, 95% CI [0.89-1.00], while a significant reduction in MI risk (RR 0.87, CI 95% [0.82-0.93]) was observed, mainly driven by trials with fibrates (RR 0.80, 95% CI [0.73-0.87]). Neither niacin nor CETP inhibitors trials showed a reduction in this parameter. Interestingly, the analysis based on the use or not of statins as background therapy showed that cardiovascular mortality and MI risk were significantly reduced in trials with no statin as background therapy (mainly fibrate trials), whereas adding a HDL-C-raising drug to a background statin therapy failed to show a clinical benefit, in line with a previous meta-analysis[6]. It is likely that fibrates may induce a positive clinical impact through their effect on triglycerides, which is most marked compared with the effect on HDL-C(only marginal) or LDL-C levels. Since increased levels of triglycerides are not associated with increased risk for coronary heart disease when adjusted for other lipid factors, it is likely that not triglycerides per se, but instead the cholesterol content in remnant lipoproteins represent an independent risk factor for ischemic heart disease[7]. Thus, since the benefit of fibrate therapy is primarily due to lowering of the atherogenic apoB-containing lipoproteins, which is reflected in lowering of plasma apoB[8], it is likely that the effect of fibrates reported in this meta-analysis is related to a possible effect on remnant lipoproteins rather than the minimal effect on HDL-C.

In a Mendelian randomization study[9], variants related to the *CETP* gene have been identified to generate a genetic risk score. The *CETP* score was associated with higher HDL-C levels, lower LDL-C and concordantly lower apoB levels and a lower risk of major vascular events; this association was similar to that observed with the *HMGCR* (the target of statins) score[9]. However, in patients with higher scores for both *CETP* and

HMGCR, HDL-C levels were additively higher, as additively lower LDL-C levels were observed; this was not true for apoB levels, which were not additively lower, and no further reduction in the cardiovascular risk was observed. This finding suggests that apoB-containing lipoproteins, more than merely LDL, may be major determinants of the cardiovascular risk and, therefore, the beneficial clinical effect of lipid-lowering drugs may be driven by their ability to reduce apoB levels[9]. If these observations are applied to intervention trials, it is conceivable that the lack of reduction in cardiovascular mortality observed in trials with CETP inhibitors (with the exception of the REVEAL), all of which had a statin as background therapy, might be related with a "negative" interaction between HMGCR and CETP inhibition, which might not lead to a reduction in apoB-containing lipoprotein level consistent enough to reduce myocardial infarction or cardiovascular mortality.

One last note of caution is to the study design which , as many other analyses recently published, relies on published averages and not on individual data. However, this does not detract from the interest of these findings.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Bibliography

1. Emerging Risk Factors Collaboration Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. *Jama* 2009; 302: 1993-2000.
2. Remaley AT, Norata GD and Catapano AL. Novel concepts in HDL pharmacology. *Cardiovasc Res* 2014; 103: 423-8.
3. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012; 380: 572-80.
4. Madsen CM, Varbo A and Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J* 2017; 38: 2478-86.
5. Riaz H, Khan SU, Rahman H, Kaluski E, Lincoff AM and Nissen SE. Effects of High Density Lipoprotein Targeting Treatments on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. *Eur J Prev Cardiol* 2018.
6. Ip CK, Jin DM, Gao JJ, et al. Effects of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events: A meta-analysis of randomized controlled trials. *Int J Cardiol* 2015; 191: 138-48.

7. Varbo A, Benn M, Tybjaerg-Hansen A, Jorgensen AB, Frikke-Schmidt R and Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *Journal of the American College of Cardiology* 2013; 61: 427-36.
8. Sniderman AD, Couture P, Martin SS, et al. Hypertriglyceridemia and cardiovascular risk: a cautionary note about metabolic confounding. *J Lipid Res* 2018; 59: 1266-75.
9. Ference BA, Kastelein JJP, Ginsberg HN, et al. Association of Genetic Variants Related to CETP Inhibitors and Statins With Lipoprotein Levels and Cardiovascular Risk. *Jama* 2017; 318: 947-56.