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EDITORIAL COMMENT

Effects of Apolipoprotein A-I/ High-Density Lipoprotein Cholesterol on Atherosclerotic Vascular Disease

Critical Impact of Atherosclerosis Disease Stage and Disease Milieu?*

Arash Haghikia, MD,[a,b] Ulf Landmesser, MD[a,b,c]

Although epidemiologic studies suggest a relation between low high-density lipoprotein cholesterol levels and an increased risk of coronary disease (1), several clinical trials over the past years aiming at raising high-density lipoprotein (HDL) cholesterol did not demonstrate a significant clinical benefit, that is, fewer cardiovascular events in patients at high cardiovascular risk (2–4).

Moreover, although experimental studies (including murine studies in early atherosclerosis) (5) have suggested a potential atheroprotective effect of HDL infusions on atherosclerosis, subsequent clinical translational studies have demonstrated that the atheroprotective properties of HDL are markedly altered in patients with established coronary disease and its risk factors (6–8). Vasoprotective properties of HDL strongly depend on the composition of its protein cargo that undergoes marked alterations and modifications in patients with coronary disease (8,9) associated with a subsequent loss of atheroprotective functions. In addition, recent human HDL infusion studies did not demonstrate a significant benefit on coronary atheroma volume (10).

In this issue of *JACC: Basic to Translational Science*, Morton et al. (11) report on marked differences between the effects of administration of apolipoprotein A-I (apoA-I), the major structural protein of HDL on atherosclerotic vascular disease between administration in early versus late atherosclerotic vascular disease (12). This study is highly relevant toward understanding the differences between the earlier experimental studies, suggesting a protective effect of HDL infusion and more recent clinical studies, demonstrating a lack of beneficial effects of apoA-I/HDL infusions in patients with later stages of atherosclerotic vascular disease. Morton et al. (11), therefore, provide clear evidence that increasing apoA-I may have stage-dependent effects on the progression of atherosclerosis. In early-stage atherosclerosis and in younger ApoE$^{-/-}$ mice apoA-I infusion was effective in preventing atheroma growth with decreased plaque macrophage content and reduced circulating inflammatory markers. However, these beneficial effects were impaired when treatment commenced on late-stage atheroma in aged recipients. Notably, isolated apoA1 from older mice with late-stage disease was less effective to induce the expression of anti-apoptotic protein Bcl-xL through phosphorylated Akt, and subsequently failed to exert anti-apoptotic effects on endothelial cells.

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Moreover, also in this issue of *JACC: Basic to Translational Science*, Vangas et al. (13) provided additional mechanistic insight on the mechanistic pathways of how apoA-I may promote healing and

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From the [a]Department of Cardiology, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany; [b]German Center for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; and the [c]Berlin Institute of Health, Berlin, Germany. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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re-endothelialization after vascular injury. The authors (13) identified reduced in-stent restenosis, improved re-endothelialization, and reduced platelet activation upon apoA1 infusion after stent implantation in the aorta of ApoE$^{-/-}$ mice as compared with nontreated mice. The apoA1 prevented the proliferation of α-actin positive smooth muscle cells, a key factor of neo-intimal hyperplasia and restenosis. Consequently, these effects led to reduced macrophage content with reduced adverse immune response after stent deployment.

Cumulatively, the findings from Morton et al. (11) support the concept of a functional loss of vasoprotective properties of apoA-I and HDL under advanced age and diseased milieu conditions. Of note, a recent report demonstrated that accumulated apoA-I in human atheromas is largely dysfunctional due to extensive oxidation by myeloperoxidase with subsequently impaired ABCA1-dependent cholesterol acceptor activity (14). Another cause of enhanced oxidized apoA-I is reduced activity of HDL-associated anti-oxidative factors such as paraoxanase-1 (6,15). In turn, oxidized apoA-I/HDL activates endothelial lectin-type oxidized LDL receptor-1, resulting in a decreased endothelial nitric oxide synthase-dependent nitric oxide production and endothelial nitric oxide synthase-associated protective signaling pathways in vascular cells (6).

CLINICAL RELEVANCE OF EXPERIMENTAL FINDINGS AND FUTURE PERSPECTIVES

The findings from Morton et al. (11) are of particular clinical interest in light of therapeutic strategies to selectively raise apoA1. Such strategies have already been tested, for example, with the agent RVX-208 in the ASSERT trial (Efficacy and Safety of a Novel Oral Inducer of Apolipoprotein A-I Synthesis in Statin-Treated Patients With Stable Coronary Artery Disease), although it failed to achieve a significant change in plaque regression in patients with coronary disease as assessed by intravascular ultrasound imaging (16). In a recent multicenter, randomized, double-blind, placebo-controlled, dose-ranging phase IIb trial including >1,200 patients with acute myocardial infarction infusion of a plasma-derived apoA-I (CSL112) had no significant impact on the risk of major adverse cardiac events through 12 months of follow-up (AEGIS-I [ApoA-I Event Reducing in Ischemic Syndromes I] trial) (17), although it has to be mentioned that the study was not powered for this endpoint. Notably, therapeutic strategies to enhance plasma apoA-I levels have only been tested in patients with established coronary atherosclerotic disease, whereas data for apoA-I raising strategies as primary prevention are missing, to date.

In conclusion, the novel studies presented in this issue provide important insights into potential different effects of apoA-I in vascular protection in early disease and later disease stages and may lead to alterations of apoA-I/HDL and thereby alter their therapeutic properties.

ADDRESS FOR CORRESPONDENCE: Prof. Dr. Ulf Landemesser, Department of Cardiology, Charité Universitätsmedizin Berlin, (Campus Benjamin Franklin), Hindenburgdamm 30, 12203 Berlin, Germany. E-mail: Ulf.Landmesser@charite.de.

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