Although plasma high-density lipoprotein (HDL) cholesterol levels correlate inversely with the incidence of cardiovascular disease, the causative nature of this relationship has been called into question by Mendelian randomization studies and several failed clinical trials involving HDL-raising drugs. Studies in humans have indicated that the macrophage cholesterol efflux capacity of HDL is a strong inverse predictor of subclinical atherosclerosis and cardiovascular disease and remains highly statistically significant after correction for HDL cholesterol levels, suggesting that HDL-C levels may be a poor surrogate for key functions of HDL mediating antiatherogenic effects. In this issue of Circulation Research, Monette et al measured acetylcholine-induced coronary artery vasodilation, an indicator of endothelial nitric oxide (NO) bioavailability, in subjects undergoing coronary angiography, and showed that the cholesterol efflux capacity of HDL correlated inversely with coronary endothelial dysfunction (ED), a key event in early atherogenesis. In contrast, HDL and low-density lipoprotein cholesterol levels did not correlate with ED. However, the HDL particle concentration, as assessed by ion mobility analysis, did correlate with HDL cholesterol efflux capacity and inversely correlated with coronary ED, leading to the conclusion that both HDL cholesterol efflux capacity and HDL particle concentration might provide clinically useful information on ED and coronary risk and further supporting that HDL-mediated cholesterol efflux is directly related to suppression of atherosogenesis in humans.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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endothelial-preserving effects of HDL and eNOS may go beyond their role in controlling coronary vasomotor function, by suppressing cytokine-induced expression of vascular adhesion molecules and endothelial inflammation.\textsuperscript{14,15} Endothelial ABCA1 and ABCG1 cholesterol efflux pathways decrease the tumor necrosis factor-\(\alpha\) and lipopolysaccharide-induced expression of vascular and intracellular adhesion molecules,\textsuperscript{11} potentially because of sustained NO production, but also likely as a consequence of decreased Toll-like receptor cell surface expression in lipid rafts, similar to macrophages.\textsuperscript{16}

As mentioned above, the Mendelian randomization approach has been used to argue that HDL is not in the causal pathway of atherosclerosis and thus that therapeutic approaches directed at HDL are bound to fail.\textsuperscript{2,17} This generalization seems to be refuted by the results of cholesterol efflux studies on HDL, such as the present work by Monette et al.,\textsuperscript{5} previous macrophage efflux studies,\textsuperscript{4,18,19} and by numerous findings in preclinical models.\textsuperscript{20} Moreover, a recent study identified a rare loss-of-function variant of \textit{SCARB1}, the gene encoding SR-BI.\textsuperscript{21} This variant was associated with increased plasma HDL-C and increased risk of coronary heart disease, recapitulating the findings in \textit{Scarb1\textsuperscript{-/-}} mice\textsuperscript{22} and indicating the key importance of HDL-mediated reverse cholesterol transport in suppressing atherogenesis.\textsuperscript{23} Together, the evidence indicates that cholesterol efflux from both endothelium and macrophage foam cells, mediated by HDL and apo AI, plays an important role in the suppression of atherogenesis. Challenges for the future include the development and further validation of clinically useful tests to evaluate HDL function, for example, involving cholesterol efflux or HDL particle number, and the refinement of therapeutic approaches that increase cholesterol efflux and reverse cholesterol transport rather than simply increasing HDL cholesterol levels.

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\textbf{Disclosures}

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\textbf{References}


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