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Although plasma high-density lipoprotein (HDL) cholesterol levels correlate inversely with the incidence of cardiovascular disease,1 the causative nature of this relationship has been called into question by Mendelian randomization studies2 and several failed clinical trials involving HDL-raising drugs.3 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,4 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 al4 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 coronary ED.5 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 atherogenesis in humans.

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Although the macrophage foam cell has recently received the lion’s share of attention in cholesterol efflux studies, this new human investigation spotlights the importance of endothelial cell (EC) cholesterol homeostasis, maintained by HDL and ATP-binding cassette (ABC) transporter–mediated cholesterol efflux pathways, in the maintenance of coronary vasomotor function. Cholesterol efflux capacity of HDL was measured using a standard macrophage assay, in which the cellular ABC transporters A1 and G1 (ABCA1 and ABCG1) promote efflux to smaller or larger HDL species, respectively.6 The same cholesterol efflux pathways have been implicated in ECs.7 Interestingly, patients’ medium and large but not small HDL particles correlated positively with cholesterol efflux capacity and inversely with ED, suggesting that cholesterol efflux mediated by ABCG1 could be important in maintaining coronary endothelial function. ABCG1, but not ABCA1, is highly expressed in cultured human aortic ECs,8 and in mice, ABCG1 and scavenger receptor BI (SR-BI) have been shown to interact with HDL to maintain the activity of endothelial NO synthase (eNOS), preserving endothelial function.7,9 In endothelium of the murine thoracic aorta, both Abca1 and Abcg1 are induced by laminar blood flow.9 Moreover, heterozygous loss-of-function mutations of Abca1 have been associated with decreased endothelium-dependent vasorelaxation in human forearm blood flow studies, and this was restored by infusions of cholesterol-poor reconstituted HDL particles.10 Finally, a recent study using an endothelial-specific knockout of the transporters in mice has shown that Abca1 and Abcg1 contribute independently and additively to protection from atherogenesis.11 Thus, it is plausible that both ABCA1 and ABCG1 have an important role in cholesterol efflux from endothelium to HDL in both mice and humans, contributing to protection from atherogenesis.

Several mechanisms linking preservation of endothelial function by HDL and cholesterol efflux have been proposed. Cholesterol efflux mediated by ABCA1 and ABCG1 decreases the cholesterol content of caveolae, relieving the inhibitory interaction of eNOS with caveolin-1.11,12 ABCG1 mediates 7-ketocholesterol efflux to HDL, suppressing the accumulation of reactive oxygen species that induce uncoupling of eNOS into inactive monomers.7 SR-BI mediates the HDL-induced phosphorylation of eNOS at Ser1177, stimulating eNOS activation, possibly depending on cholesterol efflux.13 Several sterol efflux–dependent mechanisms thus account for HDL’s capacity to preserve eNOS activity (Figure). HDL also stimulates EC NO production independent of cholesterol efflux.14 Somewhat inconsistent with the present study, it has been reported that HDL from patients with coronary artery disease has a similar capacity to induce ABCA1- and ABCG1-mediated cholesterol efflux when compared with HDL from healthy subjects but fails to stimulate eNOS activity in human aortic ECs.14 HDL from patients with coronary artery disease failed to induce eNOS phosphorylation at its activation site Ser1177 but induced eNOS phosphorylation at an inhibitory site Thr495.14 This was suggested to be partly the result of reduced HDL-associated paraoxonase activity, which increased malondialdehyde formation in HDL, thus activating endothelial lectin–like oxidized low-density lipoprotein receptor 1 and PKCβII (protein kinase CβII).14 The
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. Endothelial ABCA1 and ABCG1 cholesterol efflux pathways decrease the tumor necrosis factor-α and lipopolysaccharide-induced expression of vascular and intracellular adhesion molecules, potentially because of sustained NO production, but also like macrophage efflux studies, and by numerous findings in preclinical models. Moreover, a recent study identified a rare loss-of-function variant of SCARB1, the gene encoding SR-BI. This variant was associated with increased plasma HDL-C and increased risk of coronary heart disease, recapitulating the findings in Scarb1−/− mice and indicating the key importance of HDL-mediated reverse cholesterol transport in suppressing atherogenesis. 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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**Disclosures**

A.R. Tall is a consultant to Amgen, Arisaph, and CSL. The other authors report no conflicts.

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24. Westerterp et al HDL and Endothelial Function


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