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EDITORIAL COMMENT

Cholesterol Efflux Capacity as a Therapeutic Target

Rationale and Clinical Implications*

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The majority of efforts to halt atherosclerosis have been focused on limiting cholesterol influx into resident macrophages within the arterial wall by reducing circulating levels of atherogenic lipoproteins, which are collectively reflected by non–high-density lipoprotein cholesterol (non–HDL-C) levels. This strategy has been remarkably effective in reducing the incidence of atherosclerotic cardiovascular disease (ASCVD) in both primary and secondary prevention populations, largely through lifestyle modification and use of statin pharmacotherapies.

However, reverse cholesterol transport, which is the movement of cholesterol from tissues to the liver and out of the body, is also an important mechanism for maintaining cellular homeostasis. Cholesterol efflux from macrophages is the first critical step of reverse cholesterol transport in the arterial wall. Preclinical and limited human clinical studies support the concept that improving cholesterol efflux promotes plaque regression, shifts macrophages from pro-inflammatory to anti-inflammatory states, promotes egress of lipid-laden macrophages out of the arterial wall, and reduces atherosclerotic lesion size (1). HDL is the key mediator of cholesterol efflux and reverse cholesterol transport. Unfortunately, it has been incorrectly assumed that the cholesterol load carried by HDL, as reflected by HDL-C, also represents the dynamic efflux function of HDL particles. However, recent studies in humans have revealed that cholesterol efflux capacity is a much more robust risk marker for incident ASCVD than HDL-C and cannot be predicted by HDL-C levels. This may explain the failure of therapies that raised HDL-C quantity without improving HDL function.

Cholesterol efflux capacity assesses the movement of labeled cholesterol from standardized cells in culture to serum depleted of apolipoprotein B, making it more specific for HDL-mediated efflux (2). Efflux capacity in 2 large Caucasian American cohorts (~1,400 participants) (3,4) and a smaller Japanese cohort (~250 participants) (5) demonstrated an inverse association with prevalent coronary disease. In contrast to these studies, efflux in another cohort of approximately 1,200 Caucasian Americans showed no adjusted association with angiographic coronary stenosis (4). In addition to cross-sectional observations, several longitudinal studies assessed efflux capacity in both high- and low-risk individuals. Measurement of efflux capacity in convenience samples using angiographic cohorts yielded conflicting results; 1 in Caucasian Americans found a positive association with incident ASCVD events (4), and another in Caucasian Europeans found an inverse association with cardiovascular death (6). In contrast, 2 large population-based studies of participants at low ASCVD risk (multiethnic Americans [7] and Caucasian Europeans [8]) yielded consistent inverse associations between baseline cholesterol efflux capacity and incident ASCVD events, which were adjusted for HDL-C and HDL particle concentrations. Taken together, the relationship between efflux capacity and clinically evident coronary disease

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remains mixed among high-risk individuals, but is thus far consistent and inverse among low-risk populations, independent of HDL composition.

Several intriguing observations from these studies deserve comment. HDL-C levels appear to explain only approximately 20% to 25% of the variation in efflux capacity, suggesting that the cholesterol load of HDL particles does not fully reflect the efflux functionality of HDL particles. In addition, efflux in these studies quantified total macrophage efflux through various cholesterol transporters, 30% to 40% of which is specific to adenosine triphosphate-binding cassette transporter A1 (ABCA1) (3). The ABCA1 transporter is essential to the maturation of HDL from small, dense particles containing mostly protein (apolipoprotein A-I) to larger spherical lipoproteins containing more cholesteryl ester. In contrast, non-ABCA1 transporters play a significant role in efflux to larger mature HDL particles, resulting in high correlations with circulating HDL-C levels. Efflux via ABCA1 is promoted by lipid-poor apolipoprotein A-I, which is often termed as a "pre-beta-1" particle, and is correlated poorly with HDL-C levels (9). Intriguingly, impaired ABCA1-specific efflux in animal studies consistently leads to increased atherosclerosis, whereas impaired non-ABCA1 efflux pathways do not (10). In support of these observations, our recent population-based study used an assay more specific for ABCA1 efflux than previously used methods, and we found almost no correlation between efflux and HDL-C levels. However, there were striking inverse associations with incident ASCVD (7).

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Therefore, the study by Nicholls et al. (11), in this issue of the *Journal*, which assesses the impact of cholesteryl ester transport protein (CETP) inhibition on ABCA1- and non-ABCA1-specific cholesterol efflux sheds new light on the complexities of HDL metabolism. CETP inhibition causes an accumulation of large HDL particles loaded with cholesteryl ester, which markedly increases HDL-C levels. Studies of CETP inhibition in humans to date have suggested increases in total cholesterol efflux, largely via non-ABCA1 transporters (12–14). The current study confirmed these findings, but also found an increase in ABCA1-specific efflux and small, dense pre-beta-1 particles with CETP inhibition. Whether these novel findings were due to the specific CETP inhibitor being tested or differences in risk status across studies (low risk in the current study vs. high risk in previous studies) remains unknown. Interestingly, although pre-beta-1 levels explained 20% to 25% of the variation in ABCA1-specific efflux at baseline and on treatment, the change in ABCA1-specific efflux did not correlate with the change in pre-beta-1 levels among patients who received only CETP inhibition treatment, suggesting that much is still unknown about what governs variation in ABCA1-specific efflux. The mechanism by which CETP inhibition would increase ABCA1-specific efflux is unclear, but these observations highlight the complexity of HDL function and suggest that therapies that differentially affect macrophage efflux transporters may produce differential clinical outcomes.

The clinical relevance of manipulating the reverse cholesterol transport pathway in humans remains unknown. The failure of niacin and 2 CETP inhibitors to improve cardiovascular outcomes in addition to statins, despite increases in HDL-C, certainly dispels change in HDL-C as a valid sole therapeutic target, but it also leaves unanswered whether changes in efflux can affect outcomes. These failed therapies increased total efflux, but none increased ABCA1-specific efflux; therefore, the current CETP inhibitor tested in the current study might provide a more direct answer in ongoing outcomes trials. However, it will remain challenging to fully assess the therapeutic impact of targeting ABCA1-specific efflux in studies with concomitant statin use, which may dampen increases in efflux as the current investigation suggests, and in studies that test therapies like CETP inhibitors that not only affect HDL but also lower non-HDL-C levels. Questions that remain include what amount of change in ABCA1-specific efflux is necessary to confer clinical benefit, whether the mechanism by which a therapy changes ABCA1-specific efflux matters, and whether altering efflux will affect plaque stability and plaque regression similarly across the continuum of plaque morphology from nascent fatty streaks to calcified fibrotic plaques to lipid-laden inflammatory lesions.

In summary, measuring the dynamic functionality (efflux) versus simply the cholesterol load (HDL-C) of HDL particles imparts significantly more information about HDL metabolism. The key antiatherosclerotic function of HDL is to promote cholesterol efflux and reverse cholesterol transport, and this function has been inversely associated with ASCVD in both low- and high-risk cohorts, independent of HDL-C levels. Future studies will need to ascertain the determinants of ABCA1-specific cholesterol efflux, whether targeting ABCA1-specific cholesterol efflux will promote plaque regression and improve clinical outcomes, and if disease and treatment status modify these relationships.

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