Despite epidemiological studies showing that increased levels of high-density lipoprotein cholesterol (HDL-C) are associated with a reduced risk of future coronary heart disease, neither monogenic diseases characterized by extreme HDL-C levels nor genetic variants associated with higher HDL-C levels are associated with coronary heart disease risk reduction. Most importantly, increasing HDL-C levels as a therapeutic approach to reduce cardiovascular risk has been called into question by the recent failure of several randomized trials in which therapies aimed at increasing HDL-C levels, such as niacin and cholesteryl ester transferase protein inhibitors, have failed to improve cardiovascular outcomes.

However, it remains clear that HDL has multiple potential antiatherogenic functions, including its well-described role in reverse cholesterol transport (RCT) (Figure [A]). Thus, a novel approach toward coronary heart disease prevention and HDL-targeting therapies focuses on enhancing HDL function rather than HDL-C levels. That cholesteryl efflux capacity of HDL isolated from human subjects is inversely correlated with coronary heart disease status reinforces the concept that atheroprotection is associated with HDL function rather than HDL-C levels. This issue of *Arterioscler Thromb Vasc Biol* presents evidence that in healthy volunteers, infusion of CSL112, a reconstituted HDL (rHDL) containing apolipoprotein AI (apoAI) and phospholipids improves biomarkers of RCT and cholesteryl efflux measured ex vivo.

During the first step in RCT, lipid-poor apoAI particles (also called pre-β particles or nascent HDL) interact with the membrane-bound ATP-binding cassette transporter A1 (ABCA1) to accept free cholesterol from cells, such as macrophages in the arterial wall. The free cholesterol is then esterified by lecithin cholesterol acyltransferase to facilitate the formation of mature HDL that in turn can accept cholesteryl from other transporters. Animal studies have shown that either apoAI overexpression or treatment with a bolus of rHDL removes cholesterol from plaques reversing the atherosclerotic process. rHDL containing either apoAI Milano or wild-type apoAI results in similar plaque regression. Furthermore, high-dose single bolus rHDL infusions lead to acute plaque stabilization in animals, suggesting that a rapid, dynamic change in HDL level and efflux may lead to plaque stabilization.

Several rHDL formulations have been used in human studies. In patients with acute coronary syndrome, rHDL infusions composed of either apoAI Milano or wild-type apoAI reduced atheroma volume assessed by intravascular ultrasound compared with baseline values. However, no significant changes were found as compared with placebo groups. It is possible that in the context of acute coronary syndrome, biomarkers of plaque stability or RCT may be more relevant than atheroma volume. Interestingly, in patients with peripheral vascular disease, infusion of the CSL112 predecessor, CSL-111, resulted in decreased lipid content of excised femoral plaque as well as decreased inflammatory markers as compared with saline. Furthermore, infusion of rHDL containing a recombinant pro-apoAI has been shown to stimulate fecal steroid secretion in humans, suggesting upregulation of RCT.

The present work by Gille et al provides strong evidence that infusion of CSL112 markedly improves ex vivo cholesteryl efflux capacity, the most accurate measure of the RCT pathway available today. Although total cholesteryl efflux capacity is increased, the largest increase occurs in ABCA1-dependent efflux, which likely reflects the significant acute, dose-dependent increases in circulating pre-β particles, the preferred ABCA1 substrate. The increase in pre-β particles is likely a consequence of the participation of rHDL in HDL remodeling (Figure [B]). rHDL, with a composition similar to that of CSL112, has been shown to affect the activity of several key proteins in HDL metabolism and promote the production of pre-β particles.

As expected, the initial rise in circulating cholesterol occurs as free cholesterol, with a peak reached 2 to 4 hours after the start of the CSL112 infusion. Interestingly, the peak in cholesteryl esters is observed at 24 hours, suggesting that lecithin cholesterol acyltransferase may be a limiting factor. As esterification by lecithin cholesterol acyltransferase enhances the ability of HDL to accept cholesterol and may contribute to RCT, it would be interesting to assess whether the concomitant administration of CSL112 with recombinant lecithin cholesterol acyltransferase may enhance the amount of cholesterol mobilized over time.

A limitation of this work is that cholesterol efflux capacity measured ex vivo remains a surrogate marker of RCT. In addition, significant improvements in cholesterol efflux capacity and RCT

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may or may not result in a reduction in major adverse cardiac events in the months subsequent to an acute coronary syndrome. Studies will need to be performed in patients with acute coronary syndrome to assess the efficacy and safety of this strategy.

It is also important to consider that HDL-based therapies may have therapeutic effects extending beyond cholesterol efflux and RCT. Indeed, anti-inflammatory and nitric oxide promoting functions of HDL as well as improvements in glucose metabolism have been observed in patients receiving rHDL infusions.\textsuperscript{19,24–26} Alternatively, rHDL infusion has also been shown to have direct cardiac effects and can cause shortening of the QT interval, prolongation of which is associated with sudden cardiac death.\textsuperscript{27}

In summary, unlike other therapies that increased HDL-C levels but failed to improve clinical outcomes in randomized controlled trials, rHDL therapies have the potential to reduce coronary disease and stabilize atherosclerotic plaque by improving cholesterol efflux and RCT. Further studies will determine the safety and efficacy of CSL112 in the acute coronary syndrome population, and whether CSL112 may have a broader role in stable coronary artery disease or diseases such as type 2 diabetes mellitus, arthritis, or heart failure. Although significant work remains to be done, there is reason for optimism about this approach as a promising new therapy.

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**References**


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