Increased Coronary Heart Disease Risk Determined by High High-Density Lipoprotein Cholesterol and C-Reactive Protein: Modulation by Variation in the CETP Gene

Robin P.F. Dullaart

Epidemiological evidence strongly favors the notion that the risk of cardiovascular disease (CVD) is inversely related to the plasma high-density lipoprotein (HDL) cholesterol concentration. Low HDL cholesterol is still predictive of high CVD risk in subjects with low LDL cholesterol, as well as during statin treatment. These observational data and other studies, which show that HDL particles contain a large number of antioxidative, antiinflammatory, and antiproliferative proteins, underlie the generally held view that HDL particles have atheroprotective properties. However, evidence is accumulating supporting the concept that high HDL cholesterol levels do not always predict reduced CVD risk. The Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trial and the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk case-control study revealed that (recurrent) CVD risk is not decreased in subjects with the highest HDL cholesterol and the greatest mean HDL particle size. More recently, a high HDL cholesterol, high C-reactive protein (CRP) subgroup of individuals at increased risk for a first cardiovascular event was identified in the community-dwelling Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort using the “outcome event mapping approach,” a graphical exploratory data analysis tool that has been originally developed by Corsetti et al. Applying this analytic method to the Thrombogenic Factors and Recurrent Coronary Events (THROMBO) postinfarction cohort, the presence of a subgroup at high risk of recurrence, which is characterized by high total cholesterol and CRP levels, was reported initially. Interestingly, high HDL cholesterol was found to predict increased risk of recurrent CVD within this high-risk subgroup.

What does this study add? First, this article relevantly contributes to our growing awareness that higher HDL cholesterol levels do not necessarily translate into lower CVD risk. Although increased CVD risk related to low HDL cholesterol appears to be at least in part attributable impaired antithrombogenic properties of this lipoprotein fraction, evidence is accumulating that HDL function, in terms of modulation of inflammation and reverse cholesterol transport, is not accurately reflected by the plasma HDL cholesterol concentration as such. In this view, it is also plausible to propose the concept that in case of high CVD risk despite higher HDL cholesterol, the activities of HDL-associated...
antioxidative and antiinflammatory proteins are not sufficient to match for increased demands consequent to enhanced oxidative stress, as a result of elevated lipids contained in this lipoprotein fraction.13 Second, although the CETP B2 allele is unequivocally associated with an increase in HDL cholesterol,9,10 and the largest metaanalysis to date demonstrated an odds ratio for CVD of 0.95 per B2 allele,10 results from individual CVD outcome studies are markedly inconsistent.9 For example, in the PREVEND cohort, we showed increased primary CVD risk to be associated with the B2 allele, in particular after adjustment for HDL cholesterol.9,14 In the Regression Growth Evaluation Statin Study (REGRESS), the B2 allele was associated with increased coronary artery disease prevalence when combined with a HDL cholesterol-increasing hepatic lipase (LIPC) variant.15 Of further interest, an update from the REGRESS cohort also demonstrated a B2 allele dose-dependent increase in cardiovascular and total mortality during statin treatment.16 Thus, it appears that common variations in the CETP gene, giving rise to lower CETP levels and higher HDL cholesterol, could interact with other genes, as well as with nongenetic factors, including dysfunctional HDL, in modulating CVD risk. Obviously, the mechanisms responsible for an increased CVD risk despite high HDL cholesterol need to be defined more precisely, and the association of increased risk with the CETP B2 allele, as observed in the THROMBO study,11 should be replicated in other cohorts.

Disclosures

None.

References


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