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.

From this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Corsetti et al report on additional analyses from the THROMBO cohort, now focusing on the potential role of common variation in the cholesteryl ester transfer protein (CETP) gene (TaqIB single-nucleotide polymorphism, rs 708272; the minor B2 allele is associated with higher HDL cholesterol and lower CETP mass and activity on recurrent CVD risk. Among 767 nondiabetic subjects (77% male and 79% white), a high-risk subgroup (n=166, 56% male) was identified (recurrence rate 23.5% during a mean follow-up period of 26 months versus 13.8% in the background population). Besides 29% higher HDL cholesterol and 3-fold higher CRP levels, the high-risk subgroup individuals were also characterized by larger HDL particles, higher apolipoprotein (apo)A-I and serum amyloid A levels. Unexpectedly, no low HDL cholesterol subgroup at increased risk was identified in this cohort. The CETP genotype distribution was similar in the high-risk subgroup compared with the background population. Recurrence rates increased in a B2 allele-dependent manner in the high-risk subgroup only. Accordingly, the presence of the B2 allele (hazard ratio 2.41, P=0.041), together with high apoB levels (hazard ratio 2.64, P=0.006), independently predicted recurrent coronary risk, and presence of the B2 allele interacted with high apoB on increased risk of recurrent coronary heart disease (P=0.055). Within the high-risk subgroup, B2 allele carriers had the highest serum amyloid A levels. Additionally, the relationship of HDL subfractions with non-HDL cholesterol levels was blunted in high-risk subgroup subjects carrying the B2 allele. Although CETP activity was not measured, this would suggest that cholesteryl ester transfer from HDL toward apoB-containing lipoproteins is impaired consequent to lower CETP action. Altogether, the data provided in this article agree with the hypothesis that dysfunctional HDL (probed by a proinflammatory state [high CRP and serum amyloid A levels] combined with high HDL cholesterol) increases the risk of recurrent CVD. Variation in the CETP gene, which is associated with lower CETP mass and activity, may contribute to recurrent risk, possibly via abnormal HDL remodeling and impairment of HDL’s antiinflammatory properties. The proposed role of variation in the CETP gene on recurrent CVD risk is schematically represented in the Figure.

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 atherogenic 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...
increased HDL cholesterol need to be defined more precisely, and mechanisms responsible for an increased CVD risk despite dysfunctional HDL. Obviously, the other genes, as well as with nongenetic factors, including CETP levels and higher HDL cholesterol, could interact with common variations in the CETP gene and the implications for cardiovascular disease and its treatment: an updated analysis. Pharmacogenomics. 2008;9:747–763.


Figure. Schematic representation of the influence of common variation in the CETP gene (Tag1B polymorphism, rs708272) on increased risk of recurrent coronary events in a subgroup characterized by high HDL cholesterol and CRP. Among 767 non-diabetic subjects with established coronary heart disease (THROMBO cohort), a subgroup comprising 166 individuals (21.6%) at high risk for recurrent coronary heart disease is identified, which is characterized by high HDL cholesterol and CRP levels (hazard ratio 2.41, P = 0.041) and high apoB levels (hazard ratio 2.64, P = 0.006) predicts recurrent coronary risk. The presence of the B2 allele interacts with high apoB on increased risk of recurrent coronary heart disease (P = 0.055).

Disclosures
None.
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