**THE HIGHLY DIFFICULT LIPOPROTEIN: CONTROVERSIES AND NEW DIRECTIONS**

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Classical epidemiology has established the incremental contribution of the high density lipoprotein (HDL) cholesterol measure in the assessment of atherosclerotic cardiovascular disease risk; however, genetic epidemiology does not support a causal relationship between HDL cholesterol and future risk of myocardial infarction. Therapeutic interventions directed towards cholesterol loading of the HDL particle have been based on epidemiological studies that have established HDL cholesterol as a biomarker of atherosclerotic cardiovascular risk. However, therapeutic interventions (niacin, cholesteryl ester transfer protein inhibitors) that increase HDL cholesterol in patients treated with statins have repeatedly failed to reduce cardiovascular events. Statin therapy, particularly high-dose lipophilic statins, has been recently demonstrated to interfere with ABCA1-mediated macrophage cholesterol efflux via miR33. Unraveling the HDL puzzle will require continued technical advances in the characterization and quantification of multiple HDL subclasses, and their functional properties. Key mechanistic criteria for clinical outcomes trials with HDL-based therapies include the formation of HDL subclasses that improve the efficiency of macrophage cholesterol efflux, and compositional changes in the proteome and lipidome of the HDL particle that are associated with improved anti-oxidant and anti-inflammatory properties. These measures require validation in genetic studies and clinical trials of HDL-based therapies on the background of statins that do not diminish the efficacy of macrophage cholesterol efflux.