Accepted Manuscript

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PII: S0828-282X(16)31020-0

DOI: 10.1016/j.cjca.2016.09.012

Reference: CJCA 2277

To appear in: *Canadian Journal of Cardiology*

Received Date: 7 August 2016

Revised Date: 18 September 2016

Accepted Date: 19 September 2016

Please cite this article as: Choi HY, Hafiane A, Schwertani A, Genest J, High-density Lipoproteins – Biology, Epidemiology and Clinical Management, *Canadian Journal of Cardiology* (2016), doi: 10.1016/j.cjca.2016.09.012.

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Abstract

High-density lipoproteins (HDL) have multiple pleiotropic effects against arteriosclerosis. Most are independent of the cholesterol mass within HDL particles. Yet, HDL-Cholesterol (C) remains a biomarker to assess cardiovascular risk. While the epidemiological association between HDL-C and cardiovascular risk is strong, graded and coherent across populations, Mendelian randomization studies cast doubt on whether HDL-C is causally related to atherosclerotic cardiovascular disease (ASCVD). The apparent failure of HDL-C raising therapies (fibrates, niacin and cholesteryl ester transfer protein -CETP inhibitors) raises questions about the HDL-C hypothesis. HDL particles are heterogeneous in lipid and protein composition, and thus in size and function. Multiple factors related to oxidation and inflammation may render HDL particles malfunctional or pro-atherogenic. HDL functionality may be a preferred biomarker and therapeutic target. However, most of the beneficial events of HDL particles occur in the sub-endothelial layer of arteries and not in plasma. Here, we review the complexity and controversies surrounding HDL and ASCVD. Importantly, intimal HDL biogenesis, function and egress from the arterial wall may hold the key to unlocking the therapeutic potential of HDL.

Brief summary HDL particles are complex and heterogeneous lipoproteins that are associated with protection against ASCVD. However, the measurement of HDL-C (the cholesterol mass within HDL) may not reflect the functions of HDL, nor the events that occur in the intima of arteries, where the pleiotropic functions of HDL (cholesterol efflux from foam cells, anti-oxidant