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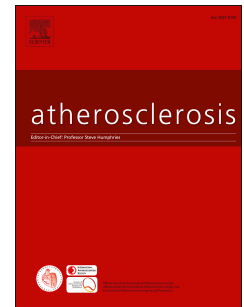
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Escaping the atherogenic trap: Preventing LDL fusion and binding in the intimaMartin Houde¹, Miranda Van Eck

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Low-density lipoprotein (LDL) cholesterol plasma concentrations have served as the target of clinical treatment of atherosclerosis-related diseases since the development of simvastatin three decades ago. Targeting endogenous cholesterol synthesis by the inhibition of β -hydroxy- β -methylglutaryl co-enzyme A (HMG-CoA) reductase, statins have since become a mainstay in the lowering of plasma cholesterol and LDL levels and the improvement of cardiovascular outcomes such as myocardial infarction and stroke. Augmented LDL-lowering with the Nieman-Pick C1-like-1 (NPC1L1) inhibitor ezetimibe or with proprotein convertase subtilisin/kexin-9 (PSCK9) inhibitors, respectively blocking exogenous cholesterol absorption or improving plasma LDL clearance, further ameliorates treatment outcomes. However, a large population of patients still experience cardiovascular events even with extremely low LDL-C concentrations [1]. Therefore, new therapeutic strategies are needed to help these patients. Studies aimed at increasing high-density lipoprotein cholesterol (HDL-C) plasma levels with niacin (vitamin B3), peroxisome proliferator-activated protein- α (PPAR- α) agonists (fibrates) and cholesterol ester transfer protein (CETP) inhibitors, and even the full length recombinant ApoA1 mimetic CER-001 provide little to no improvement of cardiovascular outcomes when added to statins [2, 3]. The failure of plasma HDL-C enhancing treatments highlighted a critical part of atherosclerotic cholesterol metabolism: lipoprotein functionality. For instance, apolipoprotein A1 (ApoA1), the main HDL apolipoprotein, can be oxidized by myeloperoxidase and proteolyzed to detrimental

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