Journal of Clinical Lipidology (2018) 12, 292–299

Journal of Clinical Lipidology

Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels—The zero-LDL hypothesis

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KEYWORDS:
Low-LDL;
PCSK9 inhibitors;
Ezetimibe;
Lipid-lowering therapy;
Low-LDL safety

Abstract: While the impact of very low concentrations of low–density lipoprotein cholesterol (LDL-C) on cardiovascular prevention is very reassuring, it is intriguing to know what effect these extremely low LDL-C concentrations have on lipid homoeostasis. The evidence supporting the safety of extremely low LDL levels comes from genetic studies and clinical drug trials. Individuals with lifelong low LDL levels due to mutations in genes associated with increased LDL-LDL receptor (LDLR) activity reveal no safety issues. Patients achieving extremely low LDL levels in the IMPROVE-IT and FOURIER, and the PROFICIO and ODYSSEY programs seem not to have an increased prevalence of adverse effects. The main concern regarding extremely low LDL-C plasma concentrations is the adequacy of the supply of cholesterol, and other molecules, to peripheral tissues. However, LDL proteomic and kinetic studies reaffirm that LDL is the final product of endogenous lipoprotein metabolism. Four of 5 LDL particles are cleared through the LDL-LDLR pathway in the liver. Given that mammalian cells have no enzymatic systems to degrade cholesterol, the LDL-LDLR pathway is the main mechanism for removal of cholesterol from the body. Our focus, therefore, is to review, from a physiological perspective, why such extremely low LDL-C concentrations do not appear to be detrimental. We suggest that extremely low LDL-C levels due to increased LDLR activity may be a surrogate of adequate LDL-LDLR pathway function.

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Submitted November 6, 2017. Accepted for publication December 20, 2017.

1933-2874/
https://doi.org/10.1016/j.jacl.2017.12.018

Introduction

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have changed the paradigm for lipid-lowering therapy to prevent cardiovascular disease. Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER), the first completed outcome study with a PCSK9 inhibitor, showed the clinical benefit of lowering low-density lipoprotein cholesterol (LDL-C) below the current goal, extending the data obtained by the IMPROVE-IT study. In the FOURIER trial, 42% of patients achieved LDL-C levels <0.65 mmol/L (25 mg/dL).[1] While the impact of very low LDL-C concentration on cardiovascular prevention is very reassuring, it is intriguing to know what effect these extremely low LDL-C concentrations have on lipid homoeostasis.

Our focus, therefore, is to review, from a physiological perspective, why such extremely low LDL-C concentrations do not appear to be detrimental. We suggest that as the LDL-LDL receptor (LDLR) pathway is the main mechanism for removal of circulating cholesterol from the body, extremely low LDL-C levels due to increased LDLR activity may be a surrogate of LDL-LDLR pathway optimization. (Complete references list in online supplementary material)

Clinical evidence for the safety of extremely low LDL-C levels

Setting the stage: Evidence from trials

The direct correlation between LDL-C levels and cardiovascular events shown by epidemiological studies is indisputable.[2] Added to this, there is a wealth of data from randomized controlled trials with statin therapy showing that lowering LDL-C levels drives cardiovascular risk reduction[3] underpinning "the lower is better" concept.[4] The Cholesterol Treatment Trialists' Collaboration showed a 22% relative risk reduction per unit LDL-C mmol/L reduction with statin therapy.[5] IMPROVE-IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: vytorin [ezetimibe/simvastatin] vs simvastatin) and FOURIER have extended the scientific evidence for the cardiovascular benefit of LDL-C reduction to <1.29 mmol/L (50 mg/dL) and <0.78 mmol/L (30 mg/dL), respectively;[1,6] therefore, the lower LDL-C threshold for benefit has not been defined yet (Fig. 1). In parallel, imaging studies provide added support[7]; in GLAGOV (GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound), patients with baseline LDL-C levels <1.8 mmol/L (70 mg/dL) attained greater atheroma regression with evolocumab against a background of high-intensity statin therapy than those with higher baseline LDL-C levels,[8] thus reaffirming the linear correlation between LDL-C lowering and reduction in the burden of coronary atherosclerosis. Indeed, current evidence shows that cardiovascular benefit is dependent on the absolute magnitude of LDL-C reduction regardless of the LDL-lowering therapy, provided that it increases LDLR activity.[9,10] What, then, is the evidence that these VLDL-C levels are safe?

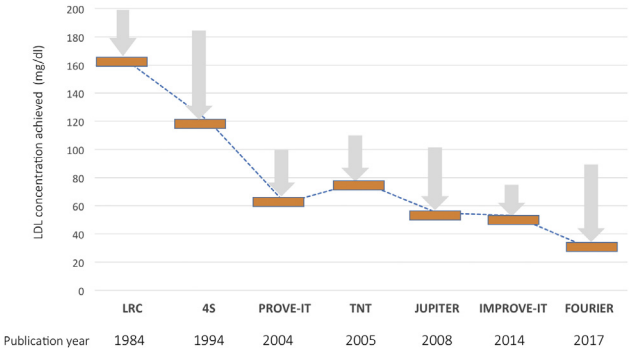

Figure 1 Historical perspective of LDL levels achieved in some of the major randomized controlled trials with lipid-lowering drugs. Arrows indicate the mean LDL decrease obtained in the study. LDL-C values from the Lipid Research Clinics are extrapolated from total cholesterol. LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol.

Living with genetically driven extremely low LDL-C levels

A number of lines of evidence offer insights into this question. LDL-C levels at birth are very low. Ethnic groups that maintain a hunter-gatherer culture have been shown to have lifelong LDL-C levels below 50 mg/dL, with no evidence of health concerns.[11] Added to this, genetic hypercholesterolemia provides a unique opportunity to evaluate the effects of lifelong exposure to low LDL-C levels. Interestingly, those genetic conditions leading to serious defects in lipoprotein formation, such as abetalipoproteinemia and classical (*apoB* gene defects) homozygous hypobetalipoproteinemia, are associated with clinical symptoms, including fat malabsorption, and digestive, hematological, and neurological symptoms, as well as ectopic fat deposition in the liver and other organs; therapies developed to block apolipoproteins (apo) B synthesis, such as mipomersen, or microsomal triglyceride transfer protein, such as lomitapide, have side effects that mirror these effects.[12] In contrast, genetic mutations resulting in accelerated LDL removal, even those leading to very low LDL levels (eg, *PCSK9* loss of function mutations compound heterozygous and *IDOL* loss of function), are asymptomatic even at levels <0.39 mmol/L (15 mg/dL) (Fig. 2).[13–15]

Individuals with variants in genes associated with increased LDLR activity (*HMGCoA R, NPC1L1, PCSK9, LDLR, ABCG7/ABCG8*) have moderate but lifelong low LDL-C levels with no evidence of any safety issues.[16,17]

Mendelian randomization studies have shown that the benefit of lifelong exposure to low LDL-C levels on cardiovascular risk is greater than that observed with