[ISSN:2582-3663]

Canadian Journal of Biomedical Research and Technology

Can J Biomed Res & Tech

September 2020 Vol:3, Issue:4

How Low is Low LDL?

Open Access **Review Article**

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Submission: August 14, 2020
Published: September 01, 2020

Introduction

Hyperlipidemia has been a pivotal topic owing to its direct correlation with risk of adverse cardiovascular events. Increased low density lipoproteins (LDL) levels have been found to exponentially increase the Cardiovascular (CV) risk. Hence treatment of these LDL levels are important to prevent CV mortality and morbidity. The American College of Cardiology/American Heart Association (NCEP IV) guidelines recommend prescription of evidence- based doses of statins independent of the LDL level 1.Interestingly, most physicians prefer treating to an LDL goal and consider 70mg/dl to be an appropriate target goal for people at the highest risk for cardiovascular disease.2However, despite achieving the target level of LDL at 70mg/dl with high-intensity statin therapy, there is still CV events and CV risk. This further attenuates the fact that maybe LDL levels of 70mg/dl need to decrease further and new threshold levels should be contemplated. Furthermore, targeting HDL and TG levels to reduce this residual risk has been proved futile *[3]*. The recentPCSK9 inhibitors havere-emphasized the discussion on further lowering of LDL and the age-old question has re surfaced: how low LDL, is in fact low enough to lead to minimum CV risk?

LDL Metabolism and Pathophysiology of Atherosclerosis

Elevated LDL is one of the single most important factor for atherosclerosis. It is the Deranged LDL metabolism, which leads to coronary artery disease. Cholesterol is an integral part of the human cell, and a particular level of LDL needs to be present to maintain the cell structural integrity and normal function. The development of atherosclerosis is actually a complicated process wherein LDL plays a crucial role. It causes endothelial damage, formation of fatty streaks and leading to atherosclerosis. Atherosclerosis, the causative factor for vascular diseases, is characterized by the presence of multiple layers of modified smooth muscles, foam cells, endothelial cells, WBCs, and lipid in the center. Many studies have now concluded that this atherosclerosis is basically due to lipid-related inflammation *[4]*.Thus theoretically we can prevent the inflammatory process of atherosclerosis by controlling all the possible risk factors- of which lowering LDL may prove to be of paramount importance.

LDL-Lowering Drugs

Statins have been the standard of care for dyslipidemia for the last decade. They inhibit the HMG-CoA reductase enzyme, the rate-controlling enzyme in the biosynthesis of cholesterol *[5]*. Statins are the mainstay of treatment to lower LDL cholesterol. They also prevent SMC migration and proliferation and impede the activation of TNF-alpha, 1L-1 beta, and other interleukins which play an active role in inflammation *[5]*. Statins have been associated with side effects like nerve damage, muscle pain and increased risk of DM, although the benefit has far outweighed any of these risks. Ezetimibe has also been used as an adjunctive medication in many patients of hyper lipidemia. It prevents the absorption of bile acid in the small intestine, lowers LDL, increases HDL slightly, and, to a little extent, lowers triglycerides. However, side effects of ezetimibe, are known, causing myalgia and abdominal pain.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

The newly introduced PCSK9 inhibitors have been a dramatic game changer for lowering of LDL levels, causes degradation of LDL receptors in the liver. Alirocumab and evolocumab are the two monoclonal antibodies directed against PCSK-9, and thus it prevents degradation of LDL receptors in the liver. These monoclonal antibodies, particularly alirocumab, have been reported to lead to various side effects like nasopharyngitis, reactions at the injection sites, flu-like symptoms, and muscle soreness *[6]*. Fibrates, bile acid binding resins, and niacin are also used for lowering LDL-cholesterol but their effects are limited and still questionable.

LDL Levels

The discussion regarding LDL levels and ACS has been a topic of discussion for the last few decades. The lowering of LDL levels in blood had a strong rationale behind it. In the historical perspective of individuals with hypobetalipoproteinemia and PCSK9 mutation and inherited natural protection from CAD was significantly noted. This is was because of low LDL and consequently lower incidence of atherosclerosis and associated events. Patients with a total deficiency of PCSK9 were reported to have LDL-C levels in the range of 15 mg/dl without having

any adverse effects from these extremely low LDL levels *[7]*. It is the drastic changes in our diet that are responsible for the rise of serum LDL level and increased incidence of atherosclerotic diseases *[8]*. The lowering of LDL in various studies and metaanalysis done worldwide showed that the LDL levels did play an integral role in prevention of atherosclerosis and thus guidelines defined a mark of LDL<70 mg/dl as an protectant level for better prognosis of individuals with CAD. The question still remained if the valve of LDL <70mg/dl was enough or further lowering of LDL was necessary. The concept of further lowering of LDL levels gained momentum after the definition of the South Asian paradox, which denotes that South Asian people are more prone to develop CAD despite having within-target LDL level. This the concept that further lowering of LDL below the existing target level help in reduction of atherosclerosis burden and CV events in those cases *[9]*.

Extremely Low LDL, Benefits and Adverse Effects

The LDL-C level of less than 50mg/dl is considered low while a level of less than 20mg/dl is considered extremely low. Intensive lipid lowering treatment has been found to hall the progression of atherosclerosis as compared to moderate lipid lowering treatment. Trials the REVERSAL, ASTEROID and SATURN reported intensive lipid lowering frequent to regresses the atheroma plaque volume *[10]*. The GLAGOV trial reported that patients who received evolocumab on a baseline treatment with statins demonstrated plaque regression in a larger number of patients ascompared to placebo (64.3% versus 47.3%) after 76 weeks of therapy *[11]*. In a retrospective analysis, coronary calcium score was reduced with the aggressive lowering of LDL *[12]*. Though the intensive lowering of LDL reduces the plaque size, there is an ongoing debate regarding its side effects. Few previous clinical trials had reported increased incidences of adverse events such as hemorrhagic strokes, dementia, depression, hematuria, and cancers with extremely low LDLC. The Dallas Heart Study, a population-based study, stretched over a period of 15 years found that a PCSK9 mutation is associated with significantly low LDL level. The literature reported a significant correlation between subjects with PCSK9 mutation and incidence of CAD. In a study, researchers were able to exhibit low incidence of CAD in population with PCSK9 mutations, with no increase in the hemorrhagic stroke or cancer. A person with a complete absence of PCSK9 has LDL level of about 15mg/dl, and there has not been any report of any adverse incidents *[13]*. Many have argued the lowering of the cholesterol levels to extremely low levels may affect brain functions. The brain in-itself contains 25% of total cholesterol of the body, and it is an essential ingredient to maintain the complex neuronal circuit. We all know that the blood-brain barrier is impermeable to circulatory cholesterol. Hence keeping this fact in mind, we can imply that the cholesterol regulation in the brain is not similar to that of extra cerebral cholesterol. So, lowering of cholesterol levels outside of the brain does not result in low cholesterols intracerebral and hence should not affect the brain functioning. On the surface, a target LDL level of less than 70 mg/dl may appear markedly low, but its cogency can be supported by a physiological rationale that we are born with an LDL level of 30-40mg/dl, and, at that time, the development of the brain is at its peak. Ray et al supported the safely of low LDL levels and reported that the reduction of LDL levels to as low as that of a neonate is safe as well as beneficial in reducing the risk of angina, Ml, or cerebrovascular disorder and total mortality *[14]*. These might be the levels to which humans are inherently adapted, and the levels ventured to be achieved *[9]*. Human brain is the most cholesterol-enriched organ but, unlike other peripheral organs, human brain is primarily dependent on de novo cholesterol synthesis rather than peripheral plasma cholesterol *[15]*. All this evidence leads to the conduction of the hypothesis that the lowering of plasma LDL does not affect the normal brain function unlike thought previously.

Evidence of Extremely Low LDL

Most of the statin trials showed an average of 31% of relative risk reduction which means that 69% of relative risk is still present. Despite the widespread use of statins, cardiovascular diseases and strokes are responsible for 25% of deaths worldwide. There is certainly need to address this residual risk. A meta-analysis by the Cholesterol Treatment Trialists (CTT) contributors reported that a reduction of 1 mmol per liter in LDL-cholesterol levels results in a consistent 20% to 25% decrease in the risk of the major cardiovascular events as well as the total mortality decreasing by 12 percent *[16]*. PROVE IT- T1MI study noted a residual CV risk of 22.4% despite reducing LDL-C to 62mg/dl. This residual risk was targeted in various studies by modulating HDL and TG levels but showed disappointing results. However, recently PCSK9 inhibitors have emerged as a promising alternative to achieve LDL levels even below the target. Statin mono therapy up regulates the PCSK9 by 25-35% on average, along with LDL receptors in hepatocytes, which counterbalances the beneficial effects of statin. Thus, PCSK9 inhibitors would also mitigate the intrinsic counterbalancing effect of statins when given in combination *[17]*. However, the dilemma that continues to trouble physicians is determining how aggressively LDL needs to be treated. After the recent pooled analysis of 14 trials by Robinson et al. which showed the safely and efficacy of alirocumab in attaining low LDL level even below 15mg/dl, this topic gains momentum *[18]*. Many trials piloted to ascertain the effects of lower-than recommended LDL levels have reported promising results. The TNT Trial was conducted to investigate the impact of very low LDL-C levels on major cardiovascular events compared with relatively higher LDL-C levels. The study revealed a highly significant reduction in the rate of major cardiovascular events with descending levels of LDL cholesterol with a decrease of 22 percent in combined cardiovascular end point (including coronary artery disease, nonfatal MI, and resuscitated cardiac arrest and a reduction of 20 percent in cardiac deaths with lower LDL levels) *[19]*. Additionally, the dreaded side effects of a very low LDL-C level such as muscle pain, hemorrhagic stroke, and death due to cancer were not increased. In a study in 2007, a group of patients with LDL-C less than 60mg/dl who also had other comorbid conditions such as diabetes mellitus or ischemic heart disease. After a follow-up period of 2.0+/-1.4 years, it was

found that statin improved survival not only in patients taking them at the baseline level but also in those who have LDL-C below 40mg/dl. Even patients without ischemic heart disease showed improved survival. However, there was no increased risk of elevated transaminases, malignancy, or rhabdomyolysis *[20]*.The JUPITER trial compared the clinical outcomes and adverse events in patients treated with rosuvastatin who attained LDL-C less than 50mg/dl and those who did not. The study revealed reduced major cardiovascular events by 65% among those attaining LDL-C<50mg/dl and by 44% for the rest of the cohort. Similarly, all-cause mortality was decreased by 46% among patients achieving LDL-C<50mg/dl and by 20% for the remaining cohort. However, there was also a higher rate of adverse events including diabetes, hepatobiliary disorders, and insomnia in patients with LDL-C<30mg/dl *[21]*. The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study conducted on patients with stroke or transient ischemic attack with atorvastatin 80mg found that the statin reduced the chances of stroke in these groups of patients but increased the incidence of hemorrhagic stroke *[22]*. On the contrary, another study carried out among subjects with a history of myocardial infarction who were treated with either 80mg simvastatin as a part of intensive statin therapy or 20mg simvastatin reported no difference regarding hemorrhagic stroke after a mean follow-up period of 6.7 years. However, myopathy cases were reported in a higher number, among 80mg simvastatin users *Robinson et al [23]*. evaluated the safety of alirocumab. They described LDL-C levels to be as low as 15mg/dl and did not report any adverse neuro cognitive event, although a non significant increase in cataract incidence seemed to be more in the group achieving LDL-C levels<25mg/dl *[21]*. In the same vein, *Sabatine et al*. did not report any significant increase in adverse reactions with very low LDL-C. Also, Prostate Cancer Prevention Trial indicated that low cholesterol is associated with reduced risk of high grade of prostate cancer *[24]*. A Retrospective Observational Study conducted in Quebec, Canada, on patients admitted with acute myocardial infarction concluded that high dose statin use might be associated with significant reduction in the cancer incidence *[25]*. The sub study of PROVE IT-TIM1 22 investigating 80mg atorvastatin versus 40mg pravastatin also proved that achieving LDL-C level below the expected level (80 to 100mg/dl) is not associated with increased adverse events *[28]*. The most recent data about safety and efficacy of low LDL comes from the FOURIER trial which showed have shown a significant reduction of LDL from a baseline value of 92 mg/dl to 30mg/dl with evolocumab. Most importantly, there was a significant decrease in the risk of major cardiovascular events without any major rise in adverse events. They reported a 17% decrease in the cardiovascular death, myocardial infarction, and stroke on lowering the LDL to 43mg/dl while reducing the LDL levels further to 22mg/dl decreased the risk to 20%. Additionally, they reported consistent clinical improvements per unit reduction in LDL *[29]*. A post hoc analysis of 10 ODYSSEY trials comparing alirocumab with the control indicated that low LDL-C was associated with a lower incidence of major adverse cardiovascular events with no significant increment in the treatment emergent adverse reactions *[16]*. Very recently, a pre specified safety analysis of improve it involving 15281 patients showed that patients with LDL level below 30mg/dl had no increased adverse events over six years' follow-up *[30]*. A recent meta analysis of the Cholesterol Treatment Trialists Collaboration (CTTC) *[31]* concluded that further lowering of LDL cholesterol below the present recommended target goals is associated with further reduction of cardiovascular risk with no significant safety risks. They found consistent benefit from lowering of the LDL cholesterol from a low level of 63 mg/dl to as low as 21 mg/dl. They noted a 21% relative risk reduction in vascular events *[32]*. These findings were similar to the observational data, which showed progressive greater coronary atherosclerotic plaque regression and lower risk of major vascular events with further lowering of LDL levels to less than 7 mg/dl [33]. However there was no evidence of increased incidence of adverse events due to such low levels of LDL.

Ongoing Studies

Low and extremely low LDL-C levels are being supported widely; however, many have raised concerns about their long-term effects, which still stands unexplored. The mystery behind the advantages and disadvantages of prolonged exposure to pharmacologically induced low LDL levels needs to be unveiled. A common finding among the LDL-lowering trials was the time lag between the onset of LDL lowering and the appearance of full clinical benefits regarding risk reduction presenting itself as another lacuna in the better understanding of the link between LDL-C lowering and CV risk reduction. The problem of the adverse effects encountered with high dose statin monotherapy for lowering LDL levels has been solved with the emergence of PCSK9 inhibitors though the cost effectiveness remains questionable. The immunogenic effects of the PCSK9 inhibitors varying from mild injection site reactions to anaphylaxis and loss of drug efficacy need to be scrutinized further. Recently SPIRE trial showed antibodies against the murine component of bococizumab in 15-20% of patients and a neutralizing antidrug antibody was seen only in 1.3% patients on alirocumab *[31]*. Poor adherence to the treatment due to multiple injections is another issue with the PCSK9 monoclonal antibodies. Atherapeutic strategy involving small (21-25 bp) interfering RNA (siRNA) targeting PCSK9 has gained our attraction recent past. Inclisiran, a novel therapeutic drug that inhibits PCSK9 through RNA interference, has shown encouraging results in an average reduction of LDL by 51% with only a 2-dose regime over a period of 9 months. This was investigated in a clinical phase 2 trial, ORION-1. The result of this trial is encouraging as ease of using this drug will be impactful as it needs only one or two injections over six-month to 1- year period *[32]*. Nevertheless, the impact on cardiovascular outcomes is yet to be studied in ORION-4. None of the studies have thus far mentioned the duration of treatment with PCSK9 inhibitors needed to maintain the risk reduction. Peptide-based anti-PCSK9 vaccines which have the potential to control LDL level for a longer duration are under trials *[33]*. Several ongoing studies are aiming to enhance our knowledge regarding the safety of low LDL and reduction in cardiovascular risk. In ODYSSEY outcomes, a placebo-controlled phase 3 trial, 18600 post-MT

patients are being randomized to alirocumab or placebo arm. It intends to compare the effects of alirocumab with placebo on the occurrence of cardiovascular events over a period of 64 months. The ODYSSEY apprise is a multicountry, multicenter phase 3 study aimed at investigating the safety of alirocumab in patients with severe hypercholesterolemia over a period of 30 months. TAUSSIG is another ongoing study designed to assess the long-term safety, tolerability, and efficacy of evolocumab in patients with severe hypercholesterolemia. Meanwhile, PACMAN-AM1 is evaluating the effects of PCSK9 inhibition on the morphology of coronary plaque in patients with acute myocardial infarction.

Conclusion

In summary, the residual risk despite achieving the current target LDL levels needs to be addressed. Although, the clinical benefits of lowering LDL have been well stated, their long term consequences are still under investigation. Many trials conducted in the past were successful in reducing the LDL levels well below the target with a consequent reduction in CV risk. Thought there is ample evidence that low LDL does protect from residual CV risk, There have also been a few studies claiming an increasing number of adverse effects with low and extremely low LDLD levels. Nevertheless, the overall opinion regarding the benefit of maintaining low / extremely low LDL using pharmacological therapy has been optimized in view of both reduction of cardiovascular events and even the risks involved. A recent study on sub analysis of the FOURIER trial concluded that patients who achieved progressively lower LDL cholesterol concentrations at 4 weeks in the FOURIER trial had progressively fewer cardiovascular events with no evidence of a plateau and with no increase in adverse events. These data support the use of intensive lipid lowering therapies to prevent recurrent cardiovascular events in high-risk patients and suggest that a lower target LDL cholesterol than recommended in current guidelines can safely be considered for the highest-risk patients.

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