MEDIBEATS
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In Lipidology

1. The Cholesterol Treatment Trialists' Collaboration meta-analysis has shown that there is a continuous linear correlation between LDL reduction and cardiovascular benefits. Thus lowering the LDL cholesterol lower is the cardiovascular events. Similarly, in the FOURIER trial, For example, it was shown that when there was a significant reduction of LDL from a baseline value of 92 mg/dl to 30 mg/dl with Evolocumab.

2. There was a 17% decrease in the primary endpoints of cardiovascular death, myocardial infarction, and stroke on lowering the LDL to 43 mg/dl and when the LDL levels were further reduced to 22 mg/dl, there was further lowering of the cardiovascular risk to 20%. Additionally, there were consistent clinical improvements per unit reduction in LDL. In the same manner, a post hoc analysis of 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 increase in the therapy associated adverse reactions.

3. Very recently, a pre-specified safety analysis of the IMPROVE-IT trial involving 15281 patients showed that of 971 patients with LDL levels below 30 mg/dl, there were no increased adverse events over six years of follow-up.

Why zero LDL hypotheses could be right?

Cholesterol is an essential molecule with many important cellular functions. However, a number of physiological and clinical observations have supported the fact of zero LDL blood levels.

1. All human cells can synthesize LDL for themselves if there is a need. Presumably, as this pathway is available to all tissues, very low levels of LDL are not associated with any known metabolic abnormalities or health concerns.

2. There are certain populations, where LDL cholesterol is found to be extremely low. Additionally, all of us are born with LDL levels below 1.0 mmol/L (40 mg/dl) a concentration sufficient to support neonatal organ formation during which cholesterol requirements are very high.

3. Lifelong LDL-C levels below 1.3 mmol/L (50 mg/dl) have been observed in hunter-gatherer societies with no evidence of related health risks.

4. Hereditary conditions, such as PCSK9 loss of function which promote LDL removal and LDL levels are <0.39 mmol/L (15 mg/dl) have not been shown to be associated with adverse ASCVD events.

5. In the FOURIER study of Evolocumab, 10% (n=2669/25 982) of patients reached LDL levels <0.5 mmol/L (19 mg/dL). This subgroup exhibited the lowest risk of cardiovascular events, and there was no significant difference in adverse events compared with those who had higher LDL on treatment (whether on active drug or placebo). In the same study, neurological and neurocognitive events were evaluated in subjects with very low LDL levels and no difference was observed with those with higher levels.

6. In IMPROVE-IT, more than 5000 patients receiving ezetimibe plus statin achieved an LDL-C <1.3 mmol/L (50 mg/dl), with approximately 1000 patients achieving levels <0.8 mmol/L (30 mg/dl). Over 7 years of follow-up, neither subgroup showed an increased frequency of side effects, including new-onset diabetes, hemorrhagic stroke or neurocognitive dysfunction.

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