MEDIBEATS
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Lipidology

Zero LDL Hypothesis

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, which was well tolerated and there was a significant decrease in the risk of major cardiovascular events without any major increase in the adverse events.

2. 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 prespecified safety analysis of the IMPROVE-IT trial involving 15 281 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.

Encouraged by these well designed and executed randomised controlled trials, there is growing scientific consensus that LDL cholesterol should in fact be zero or as low as possible.

This has been met with guarded assessment by the experts as critics point out that there are serious flaws in this hypothesis.

1. There is no long-term data on living with very low LDL available. We have at best safety data available for 5 to 7 years.

2. There have been safety concerns about some diseases which are associated with very low LDL cholesterol though never been proven till now. Very low levels of LDL cholesterol may be associated with an increased risk of cancer, haemorrhagic stroke, depression and preterm births in hypolipidemic mothers.

3. The side effects of the treating drugs may come into play when LDL is lowered to such a low level. Due to increased catabolism low LDL levels should not be compared with those due to low production rates, as in hypobeta - and abetalipoproteinemia, diseases characterised by severe symptoms because of apolipoprotein B deficiency.

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