Mini Review

Low density lipoprotein cholesterol target: Changing goal posts

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ABSTRACT

Elevated low density lipoprotein cholesterol (LDL) has been identified as one of the strongest correctable risk factors for cardiovascular disease in patients with diabetes. The reduction in cardiovascular events with pharmacological therapy aimed at LDL lowering is well documented in both primary prevention and secondary prevention. In this article, we review the evolving trend of aggressive LDL cholesterol lowering strategies.

Key words: LDL, cardiovascular disease, diabetes

Diabetes mellitus is a significant risk factor for cardiovascular disease (CVD), and mortality associated with diabetes is largely attributed to occurrence of CVD. Elevated low-density lipoprotein cholesterol (LDL) has been identified as one of the strongest correctable risk factors for CVD in patients with diabetes. Various clinical studies have convincingly proven the reduction in CVD events with pharmacological therapy aimed at LDL lowering. This has been true for both primary prevention of CVD and secondary prevention in those patients with established coronary heart disease (CHD). Studies conducted among patients with diabetes demonstrate similar efficacy in reducing CVD events.[1] The reduction in hard CVD outcomes (CHD death and non-fatal myocardial infarction) are more pronounced in diabetic individuals with higher baseline CVD risk (established CHD, elevated LDL, co-occurrence of multiple other risk factors).

On analyzing the evolution of the National Cholesterol Education Program: Adult Treatment Panel I - III (NCEP ATP I - III) guidelines, there seems to be a trend towards recommendations favoring more intense management of dyslipidemia. ATP I, published in 1988, identified LDL as the primary target of therapy and recommended a goal of less than 130 mg/dl as optimal. With accumulation of further evidence, the guidelines that followed in 1993, 2001, and the 2004 update has lowered this therapeutic goal, while still maintaining LDL as the main target of treatment. Current guidelines[2] from NCEP ATP III 2004 update recommend LDL levels of less than 100 as appropriate target for patients with a high risk of developing coronary heart disease (established CHD or CHD risk equivalents like diabetes mellitus, peripheral or cerebral vascular disease, Framingham 10 year CHD risk > 20%).

American Diabetes Association (ADA) recommendations (2012) for management of dyslipidemia in diabetes also have similar targets for LDL.[1] Pharmacological therapy with statin is recommended for all diabetic patients with overt CHD and in all diabetic patients above the age of 40 with one or more other risk factors for CHD, irrespective of their baseline LDL level. In low-risk individuals with diabetes (age < 40, no other risk factors), statin therapy is recommended if LDL is above 100 mg/dl. In diabetic patients without overt CHD, the therapeutic target for LDL is below 100 mg/dl; and in patients with overt CHD, a lower LDL level of 70 has been suggested as an option. If a drug-treated patient fails to achieve the desired level

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on maximally tolerated statin dose due to severe baseline elevations in LDL or drug intolerance, an alternative therapeutic goal of reducing the LDL levels by 30% – 40% from baseline may be considered an acceptable target. On the contrary, for a patient whose LDL level is just above 100 mg/dl, a therapeutic goal of reduction by 30% – 40% is probably more effective than lowering the LDL levels to slightly below 100 mg/dl.

Atherogenesis or atherosclerosis is the process of development of complex lesions or plaques in the arterial wall causing luminal narrowing, which may eventually lead to angina, claudication, or infarction. Cholesterol and triglycerides are transported in circulation as lipoproteins as they are not soluble in aqueous solutions. The various lipoproteins differ in the content of lipid particles they carry and associated apolipoprotein. LDL cholesterol is considered highly atherogenic and constitutes about 60% of total cholesterol. The combination of elevated LDL, elevated triglycerides (TG), low high-density lipoprotein (HDL), and presence of small LDL particles is the typical 'atherogenic dyslipidemia,' which is often found in association with diabetes. NCEP ATP III report also defines atherogenic dyslipidemia as a combination of the triad of elevated TG, low HDL, and presence of small LDL particles. Though small dense LDL particles appeared to be particularly atherogenic, the Multi Ethnic Study of Atherosclerosis and Veterans Affairs High Density Lipoprotein cholesterol Intervention Trial (VA-HIT) demonstrated that both small and large LDL strongly correlated with carotid intimal thickness and both fractions were significantly associated with CHD events. The finding of small LDL and increased risk of CVD may, therefore, be due to the increased number of LDL particles found in patients with small LDL. However, measurement of LDL particle number or size needs nuclear magnetic resonance (NMR) and is currently not a practical option for routine clinical practice.[3]

Though we have had dramatic success in reducing CHD events in patients with high LDL when treated with statins, there still remains a residual CVD risk even among those patients who have achieved their target LDL level as per current recommendations. The fact that atherosclerosis is strongly associated with very high LDL levels (< 200) has been proven; however, it is not uncommon to see occurrence of atherogenesis even with relatively normal LDL levels (90 – 130). It is unclear whether other lipoprotein fractions apart from LDL and non-HDL cholesterol can prognosticate this residual risk; data regarding effectiveness of interventions to alter these lipid abnormalities in reducing CHD events are also scarce. Studies evaluating intensive versus conventional therapy have provided more impressive reductions in CHD events with more robust lowering of LDL levels.

It has been speculated that atherosclerosis is rampant in our population because the average person's LDL level is almost double that of the normal physiological level.[4] Data from hunter gatherer populations who are still living their indigenous lifestyle demonstrate no evidence of atherogenesis even in those above 70 or 80 years of age. Their total cholesterol levels ranged from 100 to 150 mg/dl with an estimated LDL level of 50 to 75 mg/dl. The LDL levels of normal healthy neonates ranges from 40 to 50 mg/dl. Wild adult primates have LDL levels that range from 40 to 80 mg/dl. Humans are the only adult mammals with a mean LDL over 80 mg/dl. Hence, it may be inferred that the normal physiological level is actually around 50 to 80 mg/dl, and that an average level of approximately 130 mg/dl seen in the general population today may indeed be atherogenic as it is well above the expected levels.

The LDL receptor regulates plasma LDL levels. When human fibroblasts are grown in cell culture, they take up media LDL through the LDL receptor until sufficient cholesterol is internalized to meet cellular needs, following which there is down regulation of these receptors. The minimum amount of LDL cholesterol that is needed in such human fibroblast cultures is only 2.5 mg/dl.[4] Considering a correction factor of 10:1 ratio between plasma and interstitial fluid LDL levels, the implication is that a plasma LDL level of 25 mg/dl would be sufficient to supply peripheral cholesterol needs *in vivo*.

HMG-Co A (Hydroxy methyl glutaryl Co enzyme A) reductase inhibitors or statins are the drugs of choice in management of diabetic dyslipidemia as their efficacy in lowering LDL levels and reducing CHD events are backed by solid evidence. The LDL cholesterol lowering action of statins show considerable variation between different individuals, and this variable response is poorly understood. When maximally tolerated doses of statin fail to achieve the therapeutic target of LDL cholesterol, other strategies may be used as add on therapy. The primary aim of combination therapy in this setting is to achieve additional LDL cholesterol lowering. Niacin, ezetimibe, fenofibrate, and bile acid sequesterants all have LDL lowering properties and may used in conjunction with a statin. However, efficacy of such combination therapy in providing a significant increment in CVD risk reduction seen with statin monotherapy is still lacking.[5]

As more evidence has emerged in the recent years to support aggressive LDL cholesterol lowering strategies, the awaited ATP IV guidelines are expected to address this

issue. The TNT (Treating to New Targets) study,[6] IDEAL (Incremental Decrease in Events through Aggressive Lipid-lowering) study,[7] PROVE IT TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy -- Thrombolysis in Myocardial Infarction)[8] all support this hypothesis. Experts have speculated that the new ATP IV guidelines expected soon is likely to address issues like more aggressive LDL lowering for both primary and secondary prevention, and include use of hs CRP levels and other secondary targets e.g. HDL, apolipoprotein B and LDL particle concentration into the management plan.

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