STATINS; GOODS AND BADS

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Statins are considered to be the only drug among cardiovascular drug armamantarium that has shown potential to reverse atherosclerotic plaque volume. Statins blocks the critical rate-limiting enzyme HMG-CoAreductase (HMGCR) in cholesterol synthesis pathway in liver in which 3-hydroxy-3-methylglutaryl coenzyme A is transformed to mevalonate by HMGCR. Going back in 1976, the Japanese microbiologist Akira Endo started his pioneering work on fermntation and searched for a medically beneficial fungus among 6000 fermentation broths during 2 years. He and associates at the Fermentation Research Laboratories of Sankyo in Tokyo discovered that the fungus Penicillium citrinum suppressed HMG-CoA reductase enzyme as a defense mechanism against other microbes who use cholesterol for their survival[1]. Few years later Brown and Goldstein detected the strong connection between HMG-CoA reductase activity and the functioning of the LDL receptors, a discovery that won them the Nobel Prize in 1985. It was soon thereafter shown that the HMG-CoA reductase inhibition increased messenger RNA for LDL receptors in the liver and increased the density of LDL receptors on the surface of liver cells. Finally, Merck Research Laboratories synthesized and patented the first statin medication named mevinolin and later known as lovastatin.[2] This molecule was the first statin to be approved by the FDA.

Statins have both beneficial and deleterious effects. By inhibiting HMG-CoA reductase, they have a potent lipid-lowering effect that reduces cardiovascular risk and decreases mortality. Since the mevalonate pathway also influences endothelial function, the inflammatory response, and coagulation, the effects of statins reach well beyond their cholesterol lowering properties. These non lipid lowering beneficial effects are well known as pleiotropic effects. As with all drugs, statins may have adverse effects. However, the frequency of adverse effects is extremely low and, in selected patient populations, the benefits of statins considerably outweigh the potential risks.

When we say statins are good, It is mainly through its effects on different cholesterol fractions. Statins reduce levels of total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides, all considered to be bad cholesterols. On the other side, it raises the level of high density lipoprotein (HDL) cholesterol which is a good cholesterol fraction. The beneficial effects of lowering cholesterol levels with statins were confirmed in studies evaluating primary and secondary prevention of cardiovascular disease and its related morbidity and mortality [3,4]. As atherosclerosis is a complex pathogenic process, statins confer cardiovascular protection not only by reducing the cholesterol levels but also by their pleiotropic effects namely anti inflammatory, immunomodulatory and anti thrombotic effects by different mechanisms like decreasing LDL-cholesterol oxidation, promoting the stabilization of the atheroma plaque, inhibiting endothelial dysfunction and vascular smooth muscle proliferation and reducing platelet activity.

Furthermore, observational studies have suggested that statins may have improve outcomes in patients with a wide range of conditions including reduction in atrial fibrillation episodes, beneficial effects in different autoimmune disease like rheumatoid arthritis, chronic obstructive lung disease, acute respiratory distress syndrome and pneumonia. However, the causal role of statins in achieving these benefits remains to be proven.[5]

Speaking about the potential side effects, premature discontinuation is attributed to this aspect which is alarming provided the benefits of statin resulting in increased cardiovascular (CV) events. Enlisting the potential side effects, muscle related side effects, hepatitis and increased incidence of diabetes mellitus (DM) come on top of the list. While the other proposed side effects are potential to impair memory and cognition, kidney dysfunction, incraesed risk of haemorrhagic stroke and cataract formation[6,7].

Commonly observed side effect of statins is myopathy which is either by direct effects of statin on muscles or via autoimmune mechanism. The former causes self-limiting disease and is rare. Underlying suggested pathophysiology of myopathy is muscle damage by decreasing the production of ubiquinone which is a protein essential in stabilization of cell membrane and also plays an important role in mitochondrial respiratory chain. Increasing levels of sterols in muscle fiber results in toxic effects of

statins in the muscle[6]. The prevalence of musculoskeletal pain has been reported in observational studies to be 3–33% . About 1 in 10,000 cases per year develop substantial elevation in CK and just 2-3 in 100,000 cases per year develop rhabdomyolysis resulting in acute renal failure[7].

The JUPITER trial investigators stated an increase in the risk for hyperglycemia with rosuvastatin[8]. A meta-analysis suggested that 1 in 1000 patients treated with low dose statin and 1 in every 500 patients treated with moderate to high dose statin will develop DM annually[8]. Observational studies have also suggested that patients treated with statins may have an increased risk of hemorrhagic stroke. Statins have also been reported to increase serum levels of liver enzymes while rarely associated with serious liver injury[6]. These side effects although some of them are rare must be well known by physicians in order to ensure prompt diagnosis and management of their patient.

Decision in medicine relies on risk and benefit ratio. When beneficial effects are overwhelming, we accept the side effects. This holds true for statins. Believing statins as an absolutely safe drug is not correct. Side effects are there and may be important in a particular patient. So far their incidence is very low to justify statins as an extremely safe drug in cardiology practice.

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