Pros and Cons of Statin Therapy

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Cardiovascular disease (CVD) is a prime cause of human mortality worldwide,accounting for nearly 30 percent of all deaths. Annually, it causes 17 million deaths, including 7.6 million due to myocardialinfarction (MI) and 5.7 million due to stroke. Atherosclerosis accounts for the vast majority of CVDs and elevated serum cholesterol is the foremost risk factor for the development of atherosclerosis. Among the various components of total cholesterol, HDL is generally believed to be cardioprotective, whereas low and very low density lipoproteins (LDL, VLDL) and lipoprotein (a) [LP(a)] are highly atherogenic. Hyperlipidemia, in generalis considered to be a major cause of atherosclerosis which is responsible for coronary heart disease (CHD), ischemic cerebrovascular disease and peripheral vascular diseases. [1]Surprisingly,over 80 per cent of CVD deaths occur in low and middle-income countries. [2] In developing countries, it causes twice as many deaths as HIV, malaria, and tuberculosis combined. [3] India has a disproportionately higher burden of coronary artery disease (CAD) than most developing countries. Accordingto the official projections, India will have2.9 million CAD deaths in 2015, of which 1.16 million(40%) people will be less than 45 years of age. [4]

The Pros : Usefulness of statins in hyperlipidemia

Various drugs are available for the treatment of hyperlipidemia, e.g., statins, fibrates, bile acid binding resins and ezetimibe etc. However, statins (HMG-CoA reductase inhibitors) are most efficacious and best tolerated class of cholesterol lowering drugs which prevent CHD events and also reduce total mortality due to CVD. Statins are competitive inhibitors of HMG-CoA reductase enzyme which catalyzes early steps in cholesterol biosynthesis. These drugs reduce the LDL-C moderately but at higher doses they also reduce triglycerides and VLDL. Some of the statins like simvastatin also raise HDL-C levels.The 2012 Cholesterol Treatment Trials (CTT) Collaboration demonstrated a consistent 21 percent relative risk reduction in major adverse cardiovascular events (MACE) with statins, regardless of the baseline risk.[5] Cochrane review also analysed a total of 56,934 participants in18 randomized trials and showed consistent reduction in LDL-C that was associated with a significant reduction in mortality rates, CVD events, and cardiac interventions. A 31% reduction in fatal and 37% in non-fatal stroke was observed with statin therapy. [6] Various meta-analyses have shown that statin therapy is very effective in reducing the risk of cardiovascular disease in patients of diabetes and renal disorders.

Other than lipid lowering effect, statins have other pleotropic effects also e.g., they increase the synthesis of endothelial nitric oxide (NO) by stabilizing endothelial m-RNA synthase, inhibit rupture of plaque and stabilize it by inhibiting infiltration of monocyte in arterial wall, decrease inflammation and atherosclerotic changes by reducing plasma C-reactive protein and reduce platelet aggregation and fibrinogen level.[7]This therapy is associated with a decreased likelihood for atrial and ventricular arrhythmias and venous thromboembolism.[8,9] All these effects have a beneficial impact on cerebrovascular conditions.

The first statin studied in humans was mevastatin. The first statin approved for human use was lovastatin. There are six other statins available for clinical use. Among them, prevastatin and simvastatin are chemical modifiers of lovastatin where as atorvastatin, fluvastatin, rosuvastatin and pitavastatin are structurally distinct compounds. Four statins (atorvasatin, simvastatin, rosuvastatin and lovastatin) are available in India. Atorvastatin seems to be the most commonly used statin which is available as 205 different brands (100 as a single drug and 105 in the form of fixed dose combinations, FDCs). Others are rosuvaststin with 23 different brands(19 as a single drug and 2 as FDCs), simvastatin with 15 different brands (13 as single drug and 2 as FDCs) and lovaststin with 13 brands (all as single drug)[10] (Table1). The sale of statins has risen

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rapidly worldwide. According to one study, in UK the expenditure on statins increased from £20 million in 1993 to more than £500 million in 2006. [11] In India the total sell of statins in 2007 was estimated to be Rs. 300 crore. [12]

Sr. No.	Statin	Brands available	
		As single ingredient	In a fixed dose combination (FDC)
1.	Atorvastatin	100	105 (with antihypertensives, aspirin, ezetimibe and fenofibrate)
2.	Simvastatin	13	2 (with nicotinic acid and ezetimibe)
3.	Rosuvastatin	19	4 (with fenofibrate)
4.	Lovastatin	13	0

The Cons: Adverse effects of statins

Since hyperlipidemia is a chronic condition, long term use of statins has a potential to give rise to adverse drug reactions (ADRs). Many adverse effects are noted with the use of statins in different studies. The post marketing data shows an overall adverse event frequency with statins to be less than 0.5%.[13] Most of the ADRs with the use of statins are mild but some of them may be serious. Common ADRs with the use of statins are discussed below.

- **Myopathy :** It is one of the major adverse effects associated with statin therapy.[1] Myopathy is a general term for all potential muscle problems such as muscle pain or weakness and can occur with or without elevated creatine kinase (CK). Statin related myopathy is usually symmetrical, involves large proximal muscle groups and resolves within two months of discontinuation of the medication.[14] It occurs in 5% of the statin treated patient in clinical trials and 10% of patients in clinical practice.[14] The risk of severe myopathy is very low (100 per million person years).[14] The recent withdrawal of cerivastatin due to deaths from rhabdomyolysis has re-focused the risk of myotoxicity. Rhabdo myolysis is a dangerous toxicity which has caused 42 deaths from 1987 to 2001. The risk is dose dependent and increases in presence of other lipid lowering drugs like fibrates and niacin which alter statin metabolism and increase its plasma concentration.The risk of myopathy is increased several fold when used along with CYP4503A4 enzyme inhibitors like clarithromycin, ketoconazole, indinavir, ritonavir, voriconazole etc. Among the statins, fluvastatin and pravastatin has least chances of myopathy. The exact cause of statin-induced myopathy remains unknown.[15] Vitamin D insufficiency (<32 ng/ml) appears to be a possible mechanism of statin-induced myalgia as two-thirds of patients who had myalgia while on statin therapy have shown low vitamin D levels. [16]
- **Hepatotoxicity:** It is uncommon but concerns have always been raised since the introduction of statins in 1980s.[17] Asymptomatic mild elevation of serum transaminases (often self-limiting) have been reported with all statins with the incidence of about 1 to 3%. [18]Further, it is reported that only 3% of patients with early, minor elevation in serum transaminases experience subsequently apersistently significant elevation (greater than three times the upper limit of normal). [19] This elevation has been transient and has resolved spontaneously in 70% of cases even if the statins are continued in the given doses unchanged. [20] However serious hepatotoxicity extending to fatal reactions has also been reported.[21]
- **New-Onset Diabetes [NOD] :** A meta-analysis has shown about 9% increased risk of NOD with the use of statins.[22] In terms of absolute risk, 255 people treated for four years with statin therapy would result in one case of NOD (or 980 NOD per million person-years of statin therapy).[22] The risk of NOD is higher in women between 40–64 years as compared to those aged 65 or more, and is cumulative-dose dependent. [23] However, several studies have concluded that the statin-related NOD is a concern despite statin therapy having obvious benefits in cardiovascular disease.[24,25] Possible mechanisms of NOD include muscle insulin resistance, lower expression of GLUT-4 in adipocytes impairing glucose tolerance and suppression of glucose-induced elevation of intracellular Ca^{+} level.[26]
- **Peripheral neuropathy :** A modest association between peripheral neuropathy and statin use has also been reported. Evidence from four cohort studies and case reports suggests that the risk is small. [27]

- **Cataract:** Lens opacities have been seen in animal studies with high doses of statins. This has led to concerns about cataracts being caused by statins but the risk in humans seems to bevery small.[28]
- **Cognition:** Evidence of a link between use of statins and cognitive outcomes is mixed. Experimental studies support links between cholesterol intake and amyloid synthesis. Thus, patients receiving statins should have a reduced risk of dementia. However, many systemic reviews show no cognitive benefits for any statin.However, two clinical trials with statins (lovastatin in one, simvastatin in another) have shown significant worsening of cognitive indices relative to placebo.[29]
- **Insomnia :** Significant reduction in average sleep quality has been observed with simvastatin and pravastatin relative to placebo. Simvastatin is much more lipid soluble than the pravastatin. So simvastatin enters the CNS more readily and incidences of sleep disturbance have been reported more frequently with this agent as compared to pravastatin suggesting a possible direct action on the CNS. [28]
- **Gynecomastia and impotence:** Several reports of gynecomastia and impotence associated with statins have been reported. Experimental and RCT evidence shows that statins reduce testosterone in men because it reduces cholesterol synthesis which is precursor for testosterone. [30]
- **Dermatological reactions :** Rashes, dermatitis, eczema, alopecia and phototoxicity have been reported in one or other studies. [28]
- **Psychiatric effects:** Interestingly, psychosis, depression, anxiety, personality change and memory loss have been reported in various pharmacovigilance databases.Not only statin but other lipid-lowering agents have similar adverse effects.A suggested mechanism for psychiatric effects are that lowered plasma cholesterol concentration could cause alterations in central neurotransmitter function. [31]
- **Renal effects:** Among the statins, rosuvastatin (80 mg) is said to be associated with proteinuria, hematuria and isolated cases of renal failure. This is mainly due to the inhibition of tubular protein reabsorption. [1] One meta-analysis has compared the renal effects of atorvastatin and rosuvastatin but there was no significant difference in proteinuria except that a slight increase was noted with rosuvastatin. [32]
- Several other side effects have also been reported with statin therapy, such as intracerebral haemorrhage, acute kidney injury, prostate and lung cancer. However, large scale multicentre studies and meta-analyses have not shown any significant association between these incidents and the statin use. [33-36]

Conclusion

Statins are an important class of lipid-lowering drugs. The beneficial effect of statins in coronary artery disease is well established and cannot be questioned. Although the statins have an acceptable safety record, several adverse effects have noted with their use. It would be unwise to use them indiscriminately and jump blindly into something that is still new. A judicious use and a watchful eye are the essential requirements for any such drug use on a long term basis.

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