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Statins, Trends in Cardiovascular Therapeutics

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Abstract

Statin Market was valued nearly US$ 16 Billion in 2023 and is expected to reach nearly US$ 19 Billion by 2030, at a CAGR of 3% during forecast. An increase in occurrence of centripetal obesity, cardiovascular diseases and diabetes among geriatric populations are expected to drive the demand for effective treatment of high cholesterol. On average more than 50% of old adult population suffers from modest to high LDL levels, leading to myocardial infarction and stroke in affected population. The current prevalence rate of stroke, over 55 years, varies from 45 to 150/ 100,000 population. Between 51-60 years, the incidence of myocardial infarction is 15 %. Statins on long term usage lead to cardiovascular protection not only by reducing the cholesterol levels but also by decreasing LDL-cholesterol oxidation and by promoting the stabilization of the atheroma plaque. Adults aged 40 to 75 years who have 1 or more cardiovascular risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD risk of 10% or greater require statin intervention. Statins have disadvantages of causing hyperglycemia and weight gain but their overall advantage of protection in terms of CV events is more effective. The basic use of statins is in hyperlipidemia and mixed dyslipidemia, where they are used in more than 50% cases.

Keywords: Hyperlipidemia; Non-Insulin Dependent Diabetes Mellitus; Weight Gain; Rhabdomyolysis; Pleotropic Effect; Statin Intolerance

Abbreviations: WOSCOPS: West of Scotland Coronary Prevention Study; ASCVD: Atherosclerotic Cardiovascular Disease, Atherosclerosis, and Hyperlipidemia and Mixed Dyslipidemia; HPS: Heart Protection Study; MCP-1: Monocyte-Chemoattractant Protein-1; BMI: Body Mass Index; 4S: Scandinavian Simvastatin Survival Study.

Introduction

The history of statins dates back to the 1970s when Japanese researcher Akira Endo first isolated lovastatin from a fungus. This discovery laid the foundation for the development of statin drugs as cholesterol-lowering agents. The first statin to be approved for clinical use was lovastatin (Mevacor) in 1987. Subsequently, simvastatin (Zocor) and pravastatin (Pravachol) were introduced. These statins primarily targeted the enzyme HMG-CoA reductase, inhibiting cholesterol synthesis in the liver. The second generation of statins, including atorvastatin (Lipitor) and rosuvastatin (Crestor), offered greater potency and efficacy in lowering LDL cholesterol levels compared to first-generation statins. Atorvastatin and rosuvastatin became among the

most widely prescribed medications globally due to their effectiveness in reducing cardiovascular risk. High-intensity statin therapy, defined as achieving LDL reduction of ≥50%, became a cornerstone in the management of high-risk patients with established cardiovascular disease or very high LDL cholesterol levels. Atorvastatin and rosuvastatin are examples of high-intensity statins.

The evolution of statins has been guided by evidence from large-scale clinical trials and guidelines. Landmark trials such as the Scandinavian Simvastatin Survival Study (4S), the Heart Protection Study (HPS), and the PROVE-IT TIMI 22 trial have demonstrated the cardiovascular benefits of statin therapy in various patient populations.

Over the years, statins have been well-studied for their safety and tolerability profile. While some patients may experience side effects such as muscle symptoms or liver abnormalities, severe adverse events are rare. Statin therapy's overall benefit-risk profile remains favorable, particularly in high-risk individuals.

Statins possess a potentially unique antithrombotic mechanism that alters both coagulation and platelet activation. Potential drawbacks and benefits with statin therapy are well documented. The benefits outweigh the risks generally.

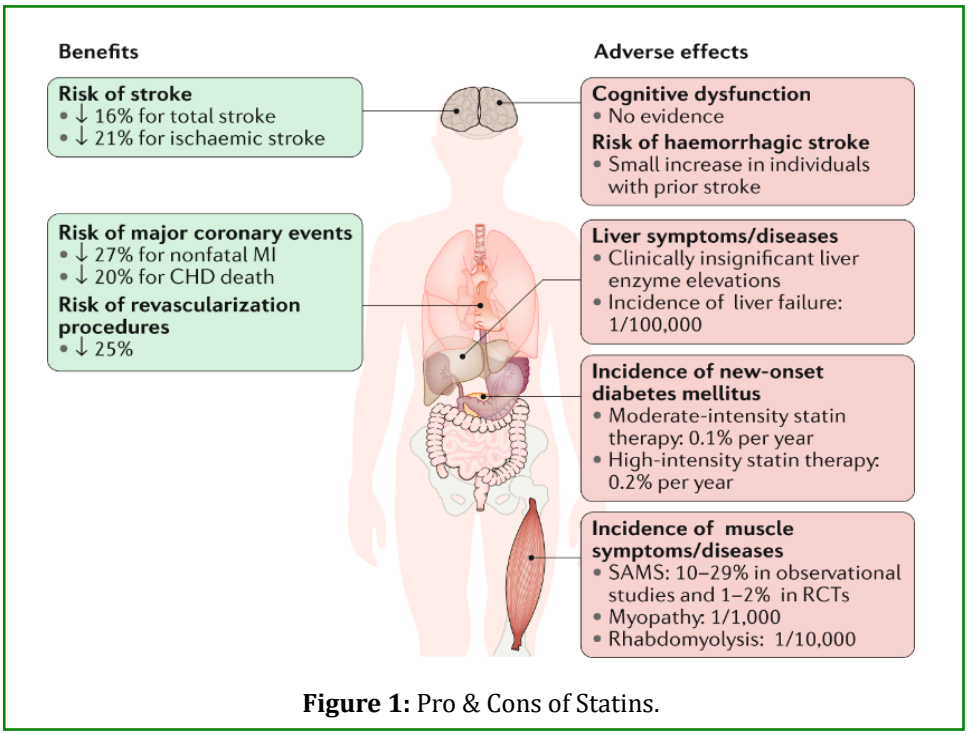

Figure 1: Pro & Cons of Statins.

Pitfalls of Statin Therapy

Hyperglycemia: The first study showing that statins were associated with the risk of T2DM was the WOSCOPS trial (West of Scotland Coronary Prevention Study). Statins have been shown to raise the risk of diabetes mellitus in that they can interfere insulin signalling pathways, affect pancreatic beta cell function and may lead to increased insulin resistance. Simvastatin, rosuvastatin and atorvastatin, produce more dysglycemia as compared to other statins. There is 48 % more risk in diabetes in middle aged women. Reduction of dysglycemia should be treated by optimum exercise, reduction of carbohydrates in diet and some cases do respond to drugs like metformin and acarbose in low doses. The Incidence of Type 2 DM was substantially larger in observational studies (55%) than in trials (11%).In patients with Type 2 DM or NIDDM, statin usage leads to increase in HbAIc and this is more with Rosuvastatin & Atorvastain. Rosuvastatin is preferred to atorvastatin in T2DM patients with dyslipidemia due to less variation in the blood sugar parameters [1-3].

Weight Gain: Statins act directly on human white adipocytes to regulate adipokine secretion and decrease leptin expression. Leptin is an important satiety factor. Hence, statin-dependent decreases in leptin may contribute, at least in part, to increase in food intake in statin users, and a weight gain is noticed over a period of one year. People who took statins ate 10% more calories and 14% more fat among statin users, body mass index (BMI) scores raised an average of 1.3 points [4].

Statin Usage and Risk of Liver Disease: Atorvastatin causes elevations in transaminases greater than 3-fold the ULN in approximately 0.5% of all cases, with an absolute risk of 1.2% with high-intensity therapy, related to immune mediated mechanism. Rarely, statins have been noted to induce more serious hepatic injury, including liver injury with autoimmune features. Statins are associated with low risk of serious liver injury. Statins, mainly atorvastatin and rosuvastatin can induce autoimmune hepatitis. The hepatitis is associated with autoimmune features marked by ANA positivity, elevations in serum immunoglobulin levels, and a clinical response to corticosteroids [5].

Statins Increase Body and Liver Fat Accumulation: Rosuvastatin, atorvastatin, fluvastatin and lovastatin administration induced and increase in adipose tissue size. That this increase was limited to the subcutaneous depot, located directly below the skin, which is less damaging than internal deposits. Statin induced increase belly fat is documented phenomenon [6,7].

Statin Intolerance is observed in patient, who is unable to tolerate a minimum of two statins at the lowest available dose. Statin intolerance occurs due to anti-HMG-CoA reductase antibodies and reduction in mevalonate pathways products like ubiquitin. Statin induced myalgia or muscle pain is commonly bilateral. It affects large proximal muscles and may worsen with exercise [8].

Cognitive Dysfunction: Post marketing reports of statins have shown a reversible cognitive impairing effect in some patients. Statins have been associated with a reduced risk of dementia and slowed progression of Alzheimer's disease [9].

Rhabdomyolysis is a well-documented side effect of statin therapy. This risk is increased with concurrent use of medications that inhibit cytochrome p450-3A4 (CYP3A4), such as macrolide antibiotics, Gemfibrozil etc. Cerivastatin was withdrawn on 8th August 2001, by Bayer Health Care, as the prescribing information had no mention about the risk of rhabdomyolysis following concurrent use of Gemfibrozil. It was evident, that 30 patients who had developed rhabdomyolysis and subsequent renal failure had consumed more than 0.4mg cerivastatin i.e. 0.8mg along with gemfibrozil. The risk of rhabdomyolysis is low, 1.5 per 100, 000 people taking statins. Statin-Induced Geranylgeranyl Pyrophosphate depletion is the cause for the same [10].

Statin use has been linked to 13 %increased incidence of cataracts, however in most studies it has not been demonstrated. Diplopia, ptosis and ophthalmoplegia have been linked in most studies [11].

1. Females – more muscle cramps are observed
2. Geriatric Toxicity
3. Hypothyroidism
4. Diabetes and its complications as Chronic kidney disease
5. Anti-epileptic drugs such as phenytoin, carbamazepine and phenobarbitone are potent inducers of cytochrome p450 enzymes and may be associated with reduced statin drug levels, therapeutically

Table 1: Precipitation of Statin Toxicity [12].

Relative Benefits of Statins: Improvement of Endothelial dysfunction is mediated by statins by following mechanisms, by causing stabilization of atherosclerotic plaques, is shown in Table below.

1. Increased synthesis of nitric oxide
2. Inhibition of free radical release
3. Decreased synthesis of endothelin-1
4. Inhibition of LDL-C oxidation
5. Reduced levels of C-reactive protein
6. Inhibition of platelet adhesion/aggregation
1. Reduced fibrinogen concentration
2. Reduced macrophage cholesterol accumulation
3. Statins increase NO bioavailability, which increases myocardial blood flow under hypoxic conditions by inhibiting IL-6, IL-8.

Table 2: Biological Mode of Action of Statins in Cardiac Events [13,14].

Thus, the approved indications for statin usage are: Primary prevention of ASCVD (atherosclerotic cardiovascular disease, Atherosclerosis, and Hyperlipidemia and mixed dyslipidemia).

LDL-C Reduction	34%	41%	48%	55%	62%
Rosuvastatin mg		5	10	20	40
Atorvastatin mg	10	20	40	80	
Simvastatin mg	20	40	80		
Lovastatin mg	40	80			

Table 3: The LDL-c Reduction is Dose Dependent and its Variable with Different Statins, Rosuvastatin is Most Potent Statin.

Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR), demonstrates Rosuvastatin better than Atorvastatin [15,16].

The anti-cancer effect of statins is closely related to their inhibitory effect on HMG-CoA reductase and mevalonate pathway. Simvastatin potentiated the anti-angiogenic effects of bevacizumab on human colorectal cancer cells [17].

Limitations of Statins

- Familial hypercholesterolemia, is not adequately managed by statins, it requires usage of PCSK 9 inhibitors, such as alirocumab. Statins confer cardiovascular protection not only by reducing the cholesterol levels but also by decreasing LDL-cholesterol oxidation.
- 51.2 per cent of patients prescribed statins show minimal benefit to their cholesterol levels within two years, leading to a significant risk of developing cardiovascular disease in the future [18].

Discussion

Statins are economical drugs, and should have a continued in the treatment of atherosclerosis due to both their immune-modulating and lipid-lowering effects. Statins target hepatocytes and inhibit HMG-CoA reductase, the enzyme that converts HMG-CoA into mevalonic acid, Statins also h inhibit hepatic synthesis of apolipoprotein B 100, their action is dose dependent. Atorvastatin reduces the number of intimal macrophages, monocyte-chemoattractant protein-1 (MCP-1) and the activation of nuclear factor NFkB. The most effective statin at reducing LDL-C is rosuvastatin 10 mg. Atorvastatin was the safest statin in relation to renal function. According to one survey, statins can reduce the relative risk of dying by 9%. Females are more likely to stop or switch their statin than men, and the main reason for this was new or worsening muscle symptoms, such as myalgia.

Conclusion

Overall, the benefits of statin therapy in reducing cardiovascular risk and lowering cholesterol levels are well-established and supported by numerous clinical trials and meta-analyses. However, like any medication, statins carry some risks, and the decision to initiate statin therapy should be individualized based on a patient's cardiovascular risk profile and potential for adverse effects. Regular monitoring and communication with healthcare providers are essential to maximize the benefits of statin therapy while minimizing risks. The U.S. Preventive Services Task Force recommends that adult's ages 40 to 75 years should be put on potent statin if they have a 10% risk of developing atherosclerosis.

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