

## STATINS-THE MOST CONTROVERSIAL DRUG OF OUR TIMES: A COMMENTARY

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### ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death worldwide. Atherosclerotic cardiovascular disease (ASCVD) is also a leading cause of death and disability. Statins can reduce the risk and prevent heart diseases. One of the best studied medication and in randomized controlled trials have been proven to reduce the no of Heart attacks and stroke even in individuals with normal cholesterol levels. A small no of individuals may develop Diabetes on statins. The benefit from lowering the risk of death, heart attack and stroke are likely to outweigh the development of diabetes in those individuals. The beneficial effects of statins may not only be due to the cholesterol lowering effects but also due to cholesterol independent or pleiotropic effects. These benefits include endothelial protective functions, enhancing stability of atherosclerotic plaques and inhibiting vascular smooth muscle proliferation and platelet aggregation. It remains to be seen to what extent these pleiotropic benefits of statin therapy can be attributed beyond cholesterol lowering.

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### INTRODUCTION

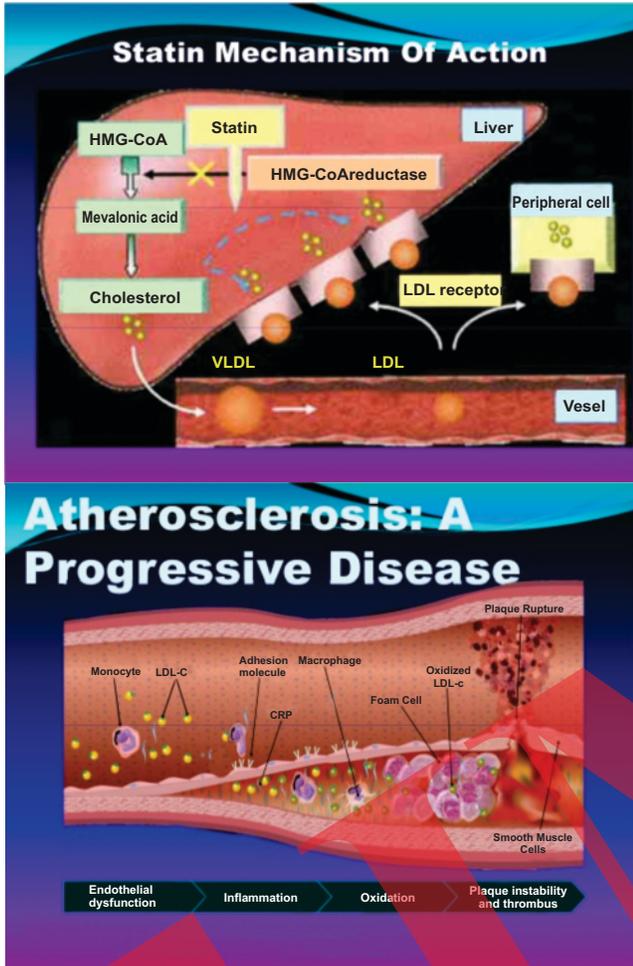
Cardiovascular disease (CVD) is the leading cause of worldwide deaths, with mortality rates of approximately 235 per 100,000 inhabitants.(1). A vast majority of the cardiovascular diseases is attributed to Atherosclerosis. High plasma cholesterol levels are thought to play a primary causative role in the development of Atherosclerotic cardiovascular diseases. Lovastatin became the first commercially available statin medication in 1987 when it was given the United States Food and Drug Administration (FDA) approval.(2) Even though it is firmly established that statins are the cornerstone of management of dyslipidemias, several controversies still exist in this area. Treatment with statins increases the risk for type 2 diabetes mellitus (T2DM) but this increase appears to be small and outweighed by the benefits of statins on cardiovascular disease prevention. Accordingly, statin treatment-associated T2DM should not affect management decisions. In patients who cannot achieve low-density lipoprotein cholesterol (LDL-C) targets despite treatment with the maximum tolerated dose of a potent statin, adding ezetimibe appears to be the treatment of choice. Finally, patients who achieved LDL-C targets with a statin but have elevated triglyceride levels appear to have increased cardiovascular risk and adding fenofibrate appears to reduce this risk. Even though additional large randomized controlled trials are unlikely to be performed with the existing lipid-lowering agents,

mechanistic, genetic and epidemiological studies, as well as careful analyses of the existing trials will provide further insights in these controversial issues and will allow the optimization of the management of dyslipidemia aiming at further reductions in cardiovascular morbidity. There has been a significant increase in the population of patients eligible for statins.

An increase in the use of statins is also thought to arise from their cholesterol-independent (pleiotropic) effects, which have implications in a wide variety of disease processes and thus may significantly broaden their therapeutic use.(3)

### THE THERAPEUTIC APPLICATION OF STATINS

There is sufficient clinical evidence of the use of Statins in the prevention of onset of atherosclerosis and its progression. As a primary prevention strategy, the use of statins allows high-risk patients to maintain normal levels of LDL-C. In patients diagnosed with ASCVD, statins are used as secondary prevention as they are effective in significantly lowering the LDL-C levels and reducing the risk of a fatal cardiovascular event. Lipoproteins are classified primarily according to their density and lipid composition and consist of the following seven major types: **chylomicrons, chylomicron remnants, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), LDL, high-density lipoproteins (HDL), and**



**lipoprotein-** (a). Chylomicrons carry dietary triglycerides and esterified and unesterified cholesterol from the intestine to the liver. While both VLDL and IDL are involved in the transport of lipids from the liver to the peripheral tissues, VLDL exports primarily triglycerides, whereas IDL exports both triglycerides and cholesterol. HDL transports both cholesterol and phospholipids but reverses the transport of the lipids by carrying them from the peripheral tissues back to the liver where they are recycled and excreted. LDL-C is often referred to as *bad* cholesterol due to its close association with ASCVD, whereas HDL-C, because of its role in reverse cholesterol transport and inverse relationship with cardiovascular incidents, is known as *good* cholesterol.(4)

#### STATIN RESISTANCE AND STATIN INTOLERANCE

While statins have proven to be advantageous for lowering the LDL-C levels in the majority of individuals, some individuals fail to respond to treatment (statin resistant) or are prone to developing AEs (statin intolerant).(5) Patients response to statins varies from 5% to 70%. Statins resistant patients do not respond to statin therapies. Statin resistance likely arises from a number of

mechanisms including polymorphisms in genes involved in cholesterol synthesis and metabolism, such as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) and low-density lipoprotein receptor (LDL-R), and those associated with statin pharmacokinetics, such as transporter proteins (eg, ATP-binding cassette sub-family G member 2 [ABCG2] and SCL01B1). Patients who are statin intolerant typically exhibit sensitivity to statin-induced myopathy and/or liver injury as indicated by increases in liver enzyme activity. In both these groups of patients other avenues for lowering of LDL-C must be sought after. Alternatives to statin therapy include use of cholesterol absorption inhibitors and bile-acid sequestrants; however, they lack the potency of statins in their ability to lower LDL-C levels. PCSK9 inhibitors is a newer treatment modality in those of high risk patient groups.(6)

#### ADVERSE EFFECTS OF USE OF STATINS

While statins, in general, are well tolerated, AEs are reported and include muscle pain and damage, increased blood glucose levels, which may contribute to type 2 diabetes mellitus (T2DM), hepatotoxicity, digestive problems, cognitive effects, and the development of rashes or flushing.(24) Of these AEs, those impacting muscle, blood glucose levels, and liver function are thought to be the most clinically relevant.

#### TYPE 2 DIABETES

The diabetogenic effects of statins are thought to arise from several mechanisms that converge on glucose regulation and pancreatic beta cells.(8,9) including inhibition of isoprenoid synthesis and subsequent inhibition of glucose uptake by beta cells, increased uptake of LDL leading to glucokinase inhibition (hence blocking glucose conversion to pyruvate), and cytokine-induced overproduction of nitric oxide (NO) leading to beta cell apoptosis. In addition, statins suppress ubiquinone and ATP synthesis. The ultimate effect of all these is the suppression of insulin production. Large no of studies have eventually reported that the as compared to the placebo group a greater no of patients eventually receiving statins therapy were subsequently diagnosed with Diabetes. Statins may have a Diabetogenic potential. While new-onset T2DM is observed with all statins, and associations coupled from those observations, a causal relationship cannot be implicated as numerous patients of the control group (receiving a placebo) also in fact developed T2DM. Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. **A collaborative metaanalysis of randomized statin**

trials had showed that Statin therapy was associated with a 9% increased risk for incident diabetes. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants. So summing up Statins therapy may be associated with slight increased risk of Type 2 Diabetes however if we compare it to the reduction in adverse coronary events statins therapy benefits outweighs the risk.

#### LIVER FUNCTION

Statin induced Liver injury is usually mild to moderate and is reversible. It usually occurs after long term use usually months to years. Statin induced Hepatotoxicity is usually a rare phenomenon. The increased Transaminases levels are usually temporary. The increased transaminases levels usually occurs due to increased membrane permeability and leakage of Liver enzymes. According to the FDA the currently marketed statins have a very Low risk of liver injury.

#### RHADOMYOLYSIS AND MUSCLE PAIN

Muscle associated symptoms in statins treated individuals occurs in 25%-30% of individuals. Patients may present with symptoms of soreness, aching and even stiffness. Clinically, these symptoms can be defined as myopathy (muscle weakness), myositis (muscle inflammation), myonecrosis (elevated muscle enzyme levels), rhabdomyolysis (severe myonecrosis with myoglobinuria or acute renal failure) and myalgia (unexplained muscle discomfort which encompasses muscle aches, soreness, etc). Mild myalgia occurs in 5%–10% of statin users annually and is often intermittent.

#### NOVEL THERAPEUTIC APPLICATION OF STATINS

Statins have been found to have pleiotropic effects. The pleiotropic effects associated with statins have been found to have an impact on disease pathophysiology include their modulation of immune responses, their enhancement of anti-inflammatory processes, and their alterations of signaling pathways. The multitude of diseases linked to the pleiotropic effects of statins include multiple sclerosis (MS), inflammatory bowel diseases (IBDs), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), chronic obstructive pulmonary disease (COPD), cancer, strokes, Parkinson's and Alzheimer's diseases, bacterial infections, and HIV. The pleiotropic effects of statins were first reported in 1995 when it was observed that the benefits of pravastatin extended beyond those attributed to the expected lipid-lowering effects of statin therapy.(10,11). Statins have been found to stabilize atherosclerotic plaque, enhance endothelial function, decreases oxidative stress and

modulate endothelial responses.

#### STATINS AND CHRONIC INFLAMMATORY DISEASES

**1.Rheumatoid arthritis**-RA is characterized by chronic inflammation of the joints, synovial hyperplasia, bone destruction, joint deformity, and systemic inflammation.(12) Patients with RA are at an increased risk of mortality, as much as 50%, due primarily to increases in CVDs. A recent meta-analysis involving 992 RA patients demonstrated that statin use significantly decreased serum levels of inflammatory markers.(13) Furthermore, patients taking statins have a reduced incidence of RA, and in those taking simvastatin and atorvastatin, a reduction in markers indicative of both RA and CVD has been reported.

**2.Statins and Inflammatory bowel diseases**-A no of animal studies have demonstrated a decrease in inflammatory markers of the diseases with statin therapy. Statins use was also associated with the decrease in the dose of corticosteroids used in the treatment of Inflammatory bowel diseases. Studies have also indicated that IBD patients on daily atorvastatin have significantly lower levels of C-Reactive proteins a marker for chronic inflammation.

**3.Statins and COPD**-The pathology of COPD, an irreversible and progressive obstruction of airflow, also involves an abnormal inflammatory response. While statins have been considered for use in treating COPD, current guidelines do not recommend the use of statins to prevent acute disease exacerbations.

#### STATINS AND CANCER

Reduction in the incidence of Colorectal cancers with Statin use was observed and this led to the speculation that statins reduces the incidence of certain cancers. There has also been reports of Statins preventing the onset of cancer and inhibiting cancer metastasis and improving patient survival. With respect to breast cancer some studies have found no association between statin use and Breast cancer mortality whereas some studies have found benefit from statin use. There have been more positive reports on prostate cancer and some reports suggests statins prevents prostate cancer progression and mortality.

#### CONCLUSION

Before considering Statins as the jack of all trades we need more substantial evidence. However the pleiotropic role of statins have opened new realm of possibilities. There are also some caveats in the use of statins. We need to identify the cohort of population who would definitely benefit from the effects of statins. The effective type, dose and duration of

therapy needs to be identified. We need biomarkers for the pleiotropic effects of statins and the measured response of the statins. There is certainly a lack of evidence on the purported benefits of statin use. We need **randomized controlled trials** for additional evidence. Till then there would always be certain grey areas in the use of statins.

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