ABSTRACT
Statins are most commonly prescribed drugs worldwide as cholesterol lowering agents. Several observational studies have shown multifaceted action in different pathological conditions by acting through cholesterol dependent as well as cholesterol independent mechanisms which affect several tissue functions. The end result is modulation of specific signal transduction pathways suggesting the ability of statins to exert pleiotropy. Pleiotropic effects or cholesterol independent effects include anti-inflammatory effects, immunomodulation, plaque stabilizing effects, anti-thrombotic, antiplatelet effects and role in vascular dysfunction. Majority of these roles are due to inhibition of a process called isoprenylation thereby preventing activation of small GTPases which are pro inflammatory signaling molecules. Here is a review of pleiotropic effects of statin therapy and their role in non-cardiac diseases.

KEYWORDS: Pleiotropy, isoprenylation, antioxidant, plaque-stabilizing, nitric oxide.

INTRODUCTION
Statins are competitive inhibitors of HMG CoA reductase that is the rate-limiting enzyme in cholesterol synthesis. They are very effective drugs and are used alone or in combination with ezetimibe, niacin or resins for managing elevated cholesterol levels. Elevated serum
aminotransferases and myopathy are important adverse effects associated with statin therapy. Lovastatin, pravastatin, simvastatin, atorvastatin and rosuvastatin are few of the drugs that belong to this class.\(^1\)

There have been many clinical trials showing the role of statins in ischemic heart failure. Surprisingly, they have also shown to improve heart function in patients with non-ischemic heart failure like in case of patients with dilated cardiomyopathy. Not limited to cardiovascular diseases, statins have also shown to improve the clinical picture in autoimmune diseases like multiple sclerosis, rheumatoid arthritis.\(^2\)

The very fact that statins inhibit HMGCoA reductase results in an inhibition of downstream effects i.e. inhibition of cholesterol biosynthesis as well as isoprenoid metabolites such as FPP (Farnesylpyrophosphate) and GGPP (Geranylgeranylpyrophosphate). Small GTPases along with isoprenoid metabolites play a central role in protein synthesis, cell signaling and multiple pathways.\(^2\)

Considering the above key role of statins, a comprehensive review of its role in cholesterol independent effects are being highlighted in this review.

**PLEIOTROPIC EFFECTS OF STATINS**

**ANTI-INFLAMMATORY EFFECTS**

Statins inhibit HMG CoA reductase, thereby inhibiting formation of intermediates like farnesyl pyrophosphate (FPP), geranyl geranyl pyrophosphate (GGPP) which are important for activation of small GTPases like Rho A, Ras, Rac and Cdc 42 which are intracellular signal molecules. FPP and GGPP act as lipid attachments for modifying these small GTPases. This process is called isoprenylation and these intermediates (FPP and GGPP) are called isoprenoids.\(^2\)

Rho A protein has two roles, one being calcium-independent smooth muscle contraction that can predispose to hypertension and coronary spasm and the other being expression of stress fibres. Rac1 causes formation of lamellipodia/ ruffles. Cdc 42 is associated with formation of filopodia.\(^2\)

Ras proteins regulate cell growth and hypertrophy\(^3\). In about 20 to 30% of tumors, Ras mutations are seen.\(^2\)
In acute inflammation, statins reduce formation of adhesion molecules, thereby affecting adhesion and migration of neutrophils from vascular compartment.\cite{4} In case of chronic inflammation, statins inhibit chemotaxis of monocytes as they interfere with monocyte chemotactic protein 1 (MCP1). Also, statins inhibit macrophage proliferation.\cite{4}

Statins reduce levels of CRP, an acute phase reactant, thereby giving evidence of anti-inflammatory effect.\cite{4}

**IMMUNOMODULATORY EFFECT**

Statins have been shown to affect antigen presenting cells (APC) by decreasing major histocompatibility factor (MHC 2) expression by inhibiting interferon gamma mediated activation of C 2 transactivator.\cite{4} Statins prevent autoimmune diseases that are tH1 mediated (graft rejection). It induces tH2 differentiation and secretion of cytokines from these cells.\cite{2} They also block adhesion molecules (ICAM-1), the end result being reduced migration and infiltration of the leukocytes and reduced T-cell activation.\cite{4}

**STATINS IN ENDOTHELIAL DYSFUNCTION**

Nitric oxide (NO) plays an important role in the endothelium. It causes vasodilation and inhibits leukocyte adhesion and platelet aggregation. It also decreases proliferation of vascular smooth muscles. Statins reduce vascular dysfunction by various modalities, as listed below.
1. LDL is said to reduce NO synthesis and bioavailability. Statins inhibit LDL synthesis thereby indirectly elevating NO levels\cite{3}

2. Statins inhibit isoprenylation of Rho that reduces eNOS gene expression, therefore statins increase NO synthesis\cite{3}

3. Statins inhibit isoprenylation of Rho thereby reducing eNOS coupling. Statins thereby increases NO synthesis\cite{3}

4. Caveolin 1 inhibits nitric oxide synthase enzyme. Statins reduce caveolin expression, thereby increasing NO synthesis\cite{3}

5. Statins upregulate heat shock protein (HSP90) and stimulate phosphatidyl inositol (PI3-akt) pathway. This results in increased expression of eNOS gene and also increased coupling, thereby promoting increased NO synthesis\cite{3}

6. Reactive oxygen species (superoxides) are said to reduce NO bioavailability by converting it into peroxynitrite. Statins inhibit NADPH oxidase, thereby reducing production of reactive oxygen species. Statins can also directly scavenge superoxide species\cite{3}

7. ADMA (Asymmetrical Di-Methyl Arginine) is an important mediator in endothelial dysfunction. ADMA reduces eNOS coupling, thereby reducing NO synthesis. Statins increases DDAH (dimethylarginine dimethylaminohydrolase), the enzyme responsible for ADMA catabolism therefore increasing NO synthesis\cite{3}
Statins cause angiotensin 1 and endothelin receptor downregulation. Endothelin and angiotensin 1 are powerful vasoconstrictors. Therefore, statins promote NO-mediated vasodilation.\[2\] By doing this, statins normalize the sympathetic outflow.\[4\]

**ANTITHROMBOTIC EFFECT**

Statins elevate tissue plasminogen activator (tPa) expression and affect expression of plasminogen activator inhibitor 1 (PAI 1), thereby rendering antithrombotic effect.

**ANTIPLATELET ACTION**

Conventionally, by reducing cholesterol content in the platelet membrane, statins impart antiplatelet action. Statins inhibit platelet aggregation by activating PPAR alpha and PPAR gamma.\[5\] Also, indirectly by increasing NO, statins impart antiplatelet activity as NO inhibits platelet activity.\[2, 6\]

**ANTIOXIDANT ACTION**

Isoprenylated small GTPases like Rac 1 are major generators of oxygen free radicals. Statins inhibit isoprenoid activation of these small GTPases, thereby inhibiting production of reactive oxygen species (ROS). Also, statins promote generation of bilirubin by inducing an enzyme called haeme oxygenase 1. Bilirubin is a powerful scavenger of superoxides. Therefore, statins inhibit synthesis and promote removal of oxygen free radicals.

**PLAQUE STABILIZING EFFECT**

A stable plaque is one that has a small core of fat and a thick cap of fibrous tissue on top of it, whereas an unstable one has a huge fatty core and fragile fibrous cap. Matrix metallo-
proteinases produced by macrophages degrade the fibrous cap, hence causing plaque rupture. Statins inhibit these MMPs, thereby providing plaque stability. Also, statins promote collagen deposition on the roof of the plaque converting the fragile cap into thick one preventing plaque rupture.[4]

STATIN WITHDRAWAL
Untoward cardiac events have been encountered when statins have been withdrawn as per data analysis done retrospectively. So it is ideal not to stop statin therapy preoperatively as it jeopardizes the health of the patients making them susceptible to intraoperative and postoperative cardiovascular events.[3] A study conducted in hemispheric stroke of ischemic etiology has revealed that statin withdrawal can lead to worsening of neurological status by an increase in infarct volume, hence increased risk of mortality.[7]

STATINS IN NON-CARDIOVASCULAR DISEASES
STATINS IN ASTHMA
A recent meta-analysis has concluded that of the 18 studies reviewed, only 3 studies showed that statins improve lung function tests whereas the other 15 have shown no improvement.[8] A preclinical study done in mice using pravastatin administered by intratracheal route has shown statins to reduce production of mucus by inhibiting hyperplasia of goblet cells. Also, there was no damage to the airway lining.[9]

STATINS IN COPD
An analysis of 9 studies that includes 6 retrospective cohorts, 2 population based analysis and 1 randomized control trial have shown that statins not only improve lung function tests but even the number of hospitalizations, intubations and mortalities reduced.[10]

STATINS IN CANCER
Statins have shown to possess beneficial role in in-vitro studies. For instance, statins (lovastatin) have shown to induce re-differentiation and apoptosis in anaplastic malignant cells of thyroid gland. Even squamous cell cancer cells have been found to be sensitive to statin-related apoptosis.[4] Statins inhibit metastasis and invasive properties of breast cancer cells as per in vitro studies.[11] Time to progression of prostate cancer is prolonged by statins. Statins reduce androgen levels within the tumour by competing with testosterone precursor dehydroepiandrosterone.[12]
STATINS IN OSTEOPOROSIS
Statins are shown to increase bone formation by increasing expression of mRNA coding for bone morphogenic protein 2 (BMP-2). It also causes BMP2 gene promoter activation.\textsuperscript{[13]}
There have also been studies which show isoprenylation as a vital factor for osteoclast activation and statins by inhibiting this isoprenylation, inhibits osteoclastic activation and activity too.\textsuperscript{[14,15]}

STATINS IN GRAFT REJECTION
Pravastatin has been shown to reduce rejection incidence in patients with cardiac transplants.\textsuperscript{[16]} Statins may also have a role in renal transplant patients as they possess immunomodulating properties.\textsuperscript{[17]}

STATINS IN VITILIGO
Vitiligo is an autoimmune disease where antibodies are targeted against melanocytes. A case report has shown high dose statin due to its immunomodulatory effect has been associated with vitiligo regression.\textsuperscript{[18]}

STATINS IN MULTIPLE SCLEROSIS
Statins have shown to reduce the movement of leukocyte into the CNS through the blood brain barrier thereby preventing demyelination. Therefore, progression of multiple sclerosis is attenuated.\textsuperscript{[19]}

STATIN IN RHEUMATOID ARTHRITIS
In animal studies, statins have been shown to lower synovial tissue inflammation.\textsuperscript{[20]} A cohort study has concluded people on statins have a lower risk to developing rheumatoid arthritis.\textsuperscript{[21]}

STATINS IN ALZHEIMER’S DISEASE
Statins have shown to modulate tau protein phosphorylation in humans. This is one way it is beneficial in Alzheimer’s disease.\textsuperscript{[22]} Also, elevated serum cholesterol levels are associated increased amyloid A-beta deposition in the brain. Statins inhibit HMG-CoA reductase, thereby reducing cholesterol. Thus, statins play an important role in altering the pathogenesis of Alzheimer’s disease.\textsuperscript{[23]}
STATINS IN DIABETES MELLITUS
Statins have been shown to elevate blood glucose levels in diabetics and also, elevate risk of developing diabetes mellitus in non-diabetics. But, at the same time, they reduce the risk of cardiovascular events.[24]

STATINS IN CONTRAST-INDUCED NEPHROPATHY
High dose statins have shown to reduce contrast-induced nephropathy in patients undergoing intervention for acute coronary syndrome.[25] Oxidative stress and inflammatory mechanisms are the main cause for contrast induced nephropathy. Statins, due to their anti-inflammatory and antioxidant effects, provide protection.[26]

STATINS AS ANTI-AGING DRUG
Statins might affect the rate of shortening of telomeres which plays a pivotal role natural aging process. This is the hypothesis supporting antiaging effect of statins.[27]

STATINS IN GLOMERULONEPHRITIS
Monocyte infiltration and VCAM1 (vascular cell adhesion molecule) expression play a very important role in pathogenesis of both atherosclerosis and glomerulonephritis. Statins, due to their immunomodulatory role, have shown an ability to inhibit monocyte activity.[28]

STATINS IN NON-PATHOLOGICAL FRACTURES
Statins have shown to exhibit a protective effect against non-pathological fractures.[29]

CONCLUSION
The evaluation of statins as therapeutic drugs depends on their efficacy. The two major problems which need to be considered in this regard are 1) they differ in solubility i.e. hydrophobic/hydrophilic rate which governs their function at extrahepatic site. 2) Dose may be higher to induce pleiotropy than that required for lipid lowering.

The concepts of pleiotropic effects of statins are concrete but their clinical applications need to be chalked out. This can be done by conducting well-planned randomized controlled trials so as to nullify the bias of existing observational study data.

In short, statins could represent a fair possibility to potentiate the conventional therapies.
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