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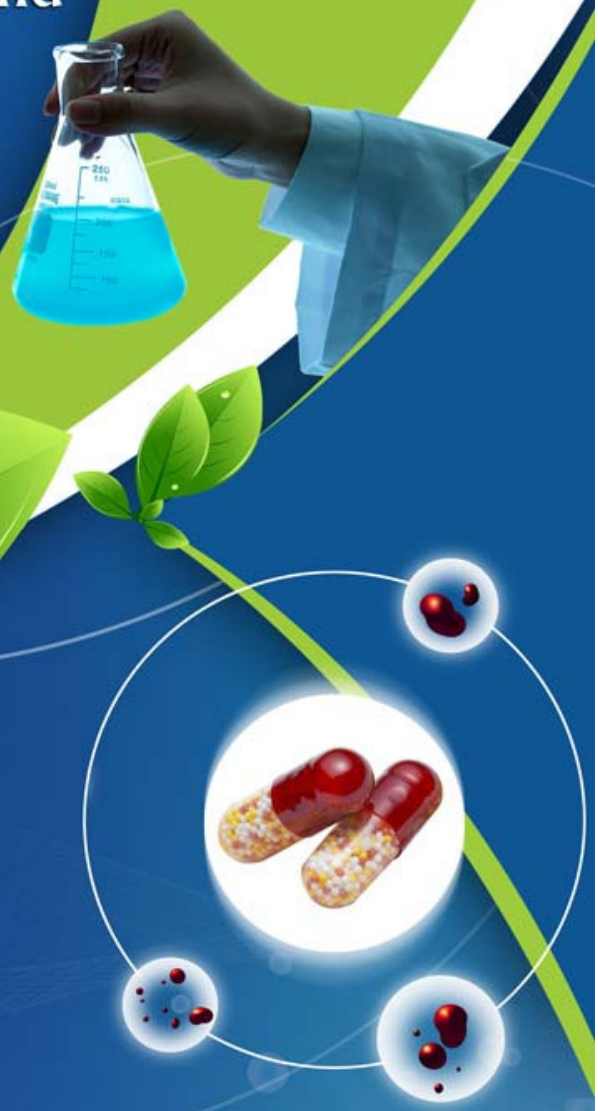

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Review Article

POSSIBLE THERAPEUTIC POTENTIAL OF STATIN INDEPENDENT OF LIPID-LOWERING ACTIVITY

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ABSTRACT

Since the discovery of the first statin nearly 30 years ago, this class of drugs has advanced to become the mainstay of cholesterol-lowering therapy to reduce the incidence of cardiovascular events in patients with or without coronary artery disease. Accumulating evidence clearly suggest that statin also induce non-lipid-modifiable action known as pleiotropic effect which could be responsible for this additional benefits. The most important positive pleiotropic effects of statins are antiinflammatory, antiproliferative, and antithrombotic effects. Statins are also directly involved in restoring or improving endothelial function, attenuation vascular remodeling, inhibition of vascular inflammatory response, and perhaps stabilizing atherosclerotic plaques. In particular, inhibition of Rho and its downstream target, Rho-associated protein kinase (ROCK), has emerged as the principle mechanisms underlying the pleiotropic effects of statins. Statins have antiatherosclerotic, antiinflammatory, antioxidant, immunomodulatory and antithrombotic effects. It applies equally to diseases of chronic inflammation type, as to those, where bone metabolism is disturbed. It is also documented that statins could decrease bone fracture risk; through bone formation intensification, and inhibition of bone tissue resorption. Slowing down the atherosclerosis progression is a very important effect, considering that in rheumatoid arthritis (RA) and in systemic lupus erythematosus (SLE) we are dealing with premature and rapid progression of atherosclerotic lesions.

Key Words: *Ststin, Pleiotropic effects, Cholesterol-lowering therapy, antiinflammatory, antiproliferative, and antithrombotic effects.*

INTRODUCTION

Statins are a group of drugs that inhibit 3-hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzyme responsible for the conversion of HMG-CoA to mevalonate, the rate-limiting step in denovo synthesis cholesterol [1]. Therefore statins are most commonly used drugs in the treatment of dyslipidemia and prevention of coronary artery disease [2,3]. Accumulating evidence clearly suggest that Statins not only inhibit the biosynthesis of cholesterol but also of isoprenoid intermediates such as geranyl-geranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) [4].

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GGPP and FPP attachments for the post-translational modification (isoprenylation) of several proteins, including the small GTP-binding proteins Ras, Rac, and Rho. [5] Isoprenylation is essential for activation and intracellular transport of proteins crucial for various cellular functions, such as maintenance of cell shape, motility, factor secretion, differentiation, and proliferation. These GTPases link the extra-cellular stimuli to signaling molecules such as mitogen activated protein kinases (MAPK) [6]. Therefore, the non-cholesterol effects of statins involve interrupting the composition of cell membranes and inhibiting protein prenylation. Statins are rapidly becoming frontline therapy for diabetes mellitus, hypertension, and other known cardiovascular disease risk factors. Originally, reductions in cardiovascular disease events and mortality and overall improved outcomes were attributed to dramatic reductions in circulating

serum lipid levels that were mediated by inhibition of liver 3-hydroxy 3-methyl glutaryl coenzyme A (HMG-CoA) reductase [7].

Statins are also known for their pleiotropic effects, which are independent of their lipid-lowering properties [3]. These pleiotropic properties includes anti inflammatory actions, improvement of endothelial function by prevention of LDL oxidation and increasing nitric oxide bioavailability. [8].Secondary to incresease expression and activity of anti-oxidant actions of statin to provide plaque stability, favourable coaugulation profile, prevention of platelet aggregation and normalizing sympathetic outflow as well as their antiproliferative and immunosuppressive properties suggest a new face of statin therapy which make them very important not only in the treatment of dyslipidemias but also in CVS and cerebrovascular diseases. [9, 10]

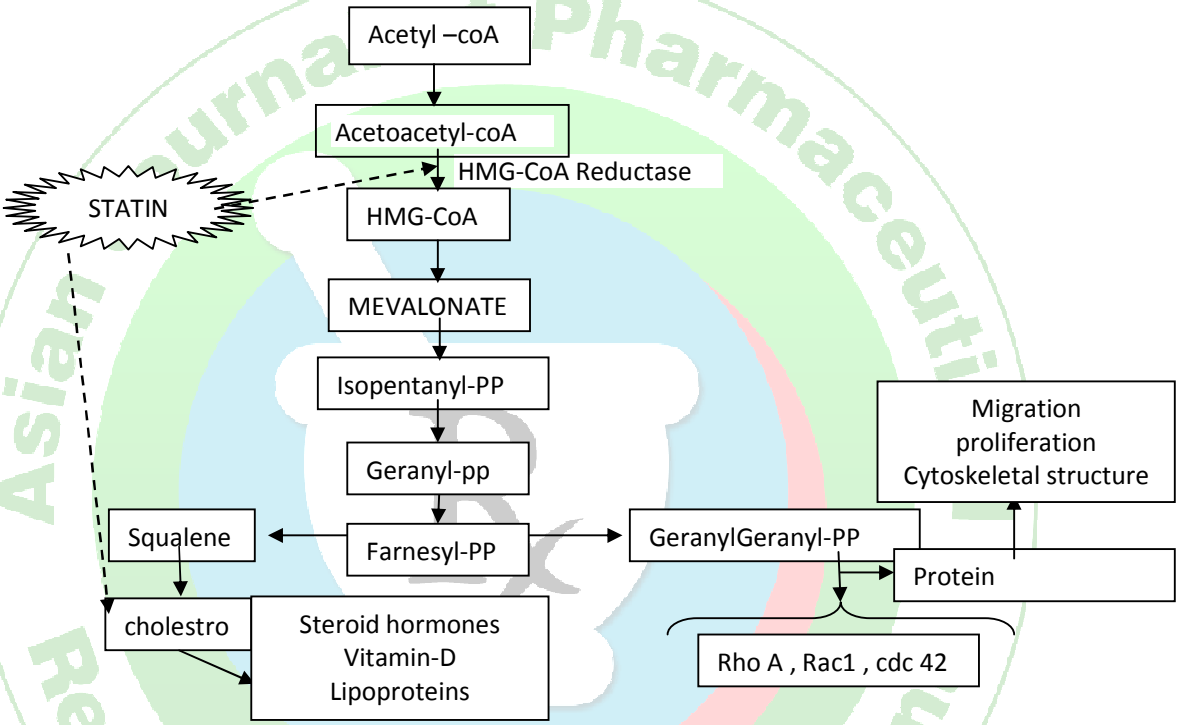

Fig 1. The endogenous mevalonate pathway leading to cholesterol biosynthesis [11]

Evidence also suggests that Statins proved to decrease stroke risk independent of LDL-cholesterol lowering effect. C-reactive protein (CRP), a marker of inflammation and are related to improved clinical outcomes and unrelated to statin effects on LDL cholesterol statins improve vascular function better than non-statin interventions that achieve similar LDL reductions

Anti Atherosclerotic Effect of Statin

Statins have capacity to decrease global fibrinolyticactivity of the blood, decrease activity of PAI-1 and inhibit thrombine generation. Data regarding influence of statins on fibrinogen levels are not so convincing. Statins shown to induce a regression in vascular atherosclerosis and a reduction also decrease the incidence of cardiovascular-related morbidity and mortality in patients with and without coronary artery disease [12-14]. Most of the effects of statins, independent of their lipid lowering activity have been correlated with their anti-inflammatory activity [15]. In addition, pleotropic effects of statins have also shown to provide therapeutic beneficial effects in various non-atherosclerotic diseases, including fibrosclerotic aortic stenosis, Sudden Cardiac Death Prevention, Arterial Hypertension Deep Venous Thrombosis, Alzheimer's Dementia, Sclerosis Multiplex, Rheumatic Diseases (RA) Osteoporosis, Regression Of Left Ventricular Hypertrophy [16]

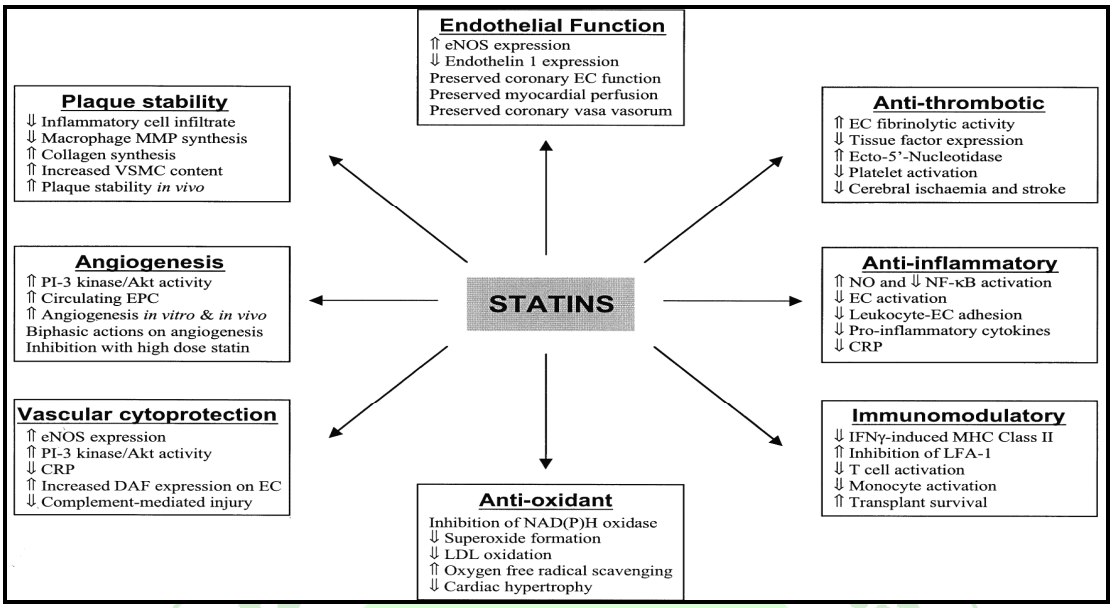

Fig 2. Various Pleiotropic properties of statins [17]

Most of which can result from their capacity to interfere with mevalonate pathway and subsequent inhibhition of prenylation of Rho family GTPases [18-21]. Macrophages are capable of degrading the extracellular matrix and, by secreting matrix metalloproteinase (MMP) which may weaken the fibrous cap and thus predispose an atheromatous plaque to rupture. Fluvastatin and simvastatin are shown to inhibit MMP-9 (gelatinase B) activity and secretion by macrophages [22]. This effect is reversed by the addition of mevalonate, suggesting that it is mediated by HMG CoA reductase inhibition. Fluvastatin appears to decrease MMP-1 expression in human vascular endothelial cells. This effect is also seen with lovastatin and again is completely blocked by co-incubation with mevalonate [23]. Simvastatin has been shown to reduce macrophage superoxide formation, thereby decreasing cell oxygen production [24]. Fluvastatin and lovastatin bind to phospholipid on the surface of LDL and thus prevent diffusion into the lipoprotein core of free radicals generated under oxidative stress [25]. In addition atorvastatin and fluvastatin have also been shown to have direct antioxidant activity [25,26]. Statins could directly upregulate endothelial nitric oxide synthase (eNOS) expression in vitro [27]. A significant increase in endothelium-dependent vasodilation in patients with moderate hypercholesterolemia has been observed after 4 weeks of treatment with simvastatin [28]. The neuroprotective effect of statins is absent in eNOS deficient mice, suggesting that enhanced eNOS activity by statins is a main mechanism by which HMGCoA reductase inhibitors protect against cerebral injury [29]. Several invitro and invivo studies shown that statin reduce cell surface expression of cell adhesion molecule (ICAM-1, LFA-1, CD11b, CD18 and CD49) on monocytes and activated T cells [30,31]. In addition, statins inhibit cell surface expression of ICAM-1, VCAM-1, LFA-1 and CD18 on activated endothelial cells [32,33]. Statins also shown to inhibit the production of pro-inflammatory cytokines such as IFN-g, TNF-a, IL-1band IL-6 by mononuclear cells, microglia and astrocytes [34-36]. In addition, statin shown to reduce serum levels of TNF-a, IL-6, IL-1 and IL-8 are lowered in hypercholester-olemic patients. [37]. Several studies have shown that statins inhibit the production of MCP-1 (CCL2) in a variety of cell types and decrease serum levels of this chemokine and IL-8 (CXCL8) in hypercholesteremic patients [37-39]. In addition treatment with Atorvastatin decrease spontaneous release of MIP-1a (CCL3) and IL-8 by PBMC is decreased in patients with coronary artery disease [40]. Various in-vitro and in-vivo experiment findings suggest that statins also exert anti-inflammatory via regulating of the immune system. The first clinical evidence showing that pravastatin

significantly decreases in the incidence of severe acute heart transplantation rejections [41]. The immunomodulatory properties of statins could be exerted through interference in the expression and function of a variety of immune relevant molecules. Numerous studies clearly evidencing that statins may affect the function of the immune and inflammatory cells, including natural killer cells, monocytes, macrophages, microglia and T cells [42, 43]. Statins shown to attenuate the secretion of pro-inflammatory cytokine interleukins (IL-1, 2, 4, 5, 10 and 12), interferon-γ, and tumor necrosis factor-α(TNF-α), decrease the activity of cyclooxygenase-2 (COX-2), thromboxanes A2, and thromboxanes B2 [2]. Simvastatin, lovastatin, atorvastatin and pravastatin were found to inhibit particularly IFN-g-induced expression of MHC-II molecules on endothelial cells, macrophages and microglia [44, 45]. In addition, they were also found to inhibit constitutive MHC-II expression on B lymphocytes and MHC-II expression by activated T lymphocytes and microglia [30,11,46,47]

In a pilot short-term comparative (simvastatin versus chloroquine) open clinical trial in 15 patients with rheumatoid arthritis shown that 90% of the patients who received simvastatin (40 mg/day) showed better response after 8 weeks, as compared to to chloroquine therefore statin are being suggested as alternative therapeutic agent for the treatment of RA [48]. Clinical studies also demonstrate that low-dosage simvastatin significantly reduce blood Th1/Th2 and CD4/CD8 ratios in RA [49]. Additional evidence that statins may have an anti-inflammatory effect is provided by a randomized trial that found that patients with rheumatoid arthritis experienced clinical improvement, reduced CRP levels and lower erythrocyte sedimentation rates when treated with atorvastatin compared with placebo [50]. In vitro studies have shown that statins inhibit protein prenylation on T-cells, and the receptor activator of nuclear factor kappa B ligand, known as RANKL, and tumor necrosis factor α (TNF-α) stimulateddifferentiation of progenitor cells into osteoclasts, resulting in a dramatic impairment in the pathways regulated by small GTPases [51,52].

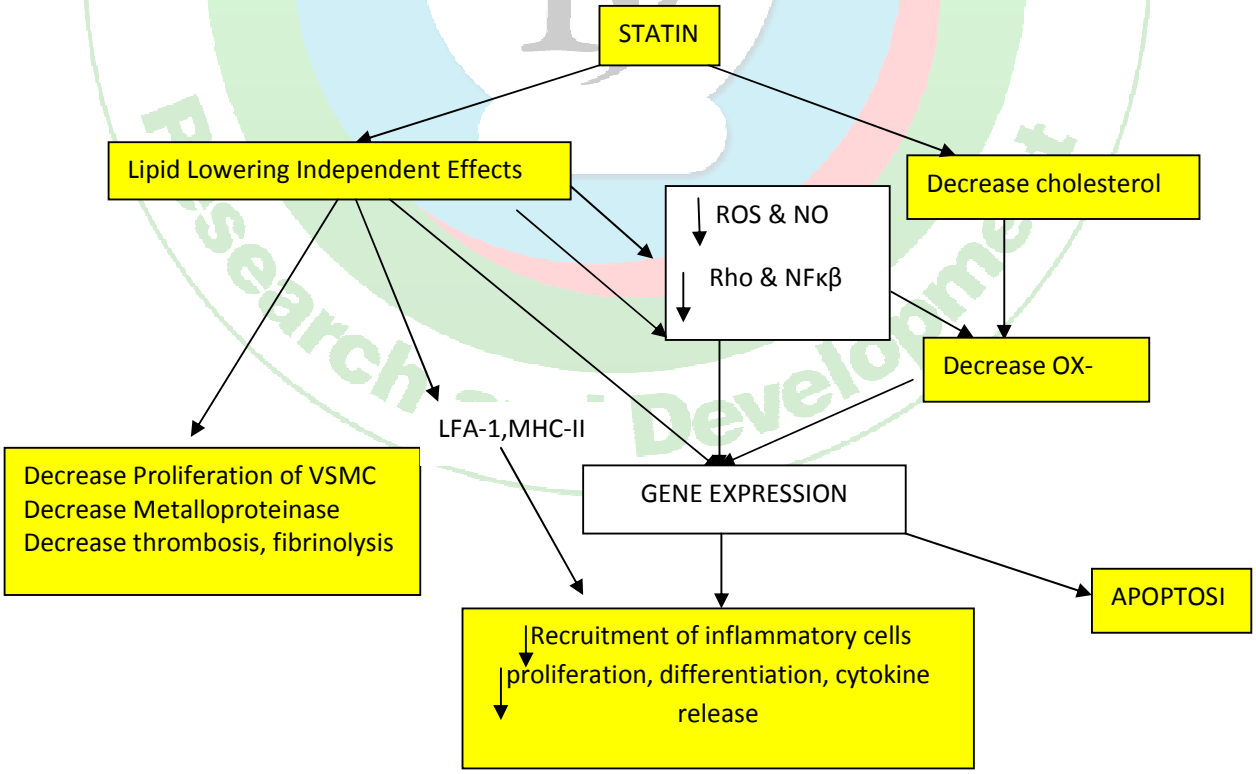

Fig 3: Anti-inflammatory actions of statins [53]

The direct anti-inflammatory effect of simvastatin (3-10 mg/kg p.o) has been demonstrated using an established model of acute inflammation i.e carrageenan-induced

foot pad edema in rat [54]. also a study has shown that atorvastatin (30 mg/kg for 14 days) could delay the progression of established autoimmune disease in the NZB/W spontaneous murine model of SLE [46]. Treatment with atorvastatin resulted in a significant reduction in anti-dsDNA antibodies, proteinuria, glomerular Ig deposition and glomerular hypertrophy. These effects were along by a significantly reduced expression of major histocompatibility complex (MHC)II and CD86/80onB-lymphocytes and consequently autoreactive T-cell proliferation was profoundly impaired. [55] Several studies have demonstrated anti-inflammatory effects of atorvastatin in normoglycemic animal models and cell culture studies [56]. Moreover, atorvastatin has been shown to reduce in vitro levels of circulating soluble ICAM-1 and VCAM-1[57]. Atorvastatin sufficiently reduce inflammatory response due to diabetes mellitus despite of hyper-glycemia and hyperlipidemia resulting in improved vascular function indexed by enhanced endothelial-dependent vasodila-tationin vivo. Taken together, NF-κB activation due to reactive oxygen species generation [58] is involved in the induction of vascular inflammatory responses including enhanced cytokines and cellular adhesion molecules expression [59] consequently resulting in endothelial dysfunction [60] which was mitigated by low-dose atorvastatin treatment. Treatment with atorvastatin at a low dose in severe diabetic conditions shown to anti-oxidative and anti-inflammatory effects including a reduced activity of the ERK1/2-NFκB-pathway, contributing to vascular protection despite unchanged levels of hyperglycemia and hyperlipidemia [61].

Statins have been shown to reduce NAD(P)H-dependent superoxide formation by a monocyte-derived cell line in culture [62]. Experiments with human endothelial cells have shown that statin treatment can inhibit ox LDL-induced NADPH oxidase expression and superoxide anion formation [63]. Atorvastatin also suppressed reactive oxygen species generation due to under diabetic conditions despite of hyperglycemia and hyperlipidemia in-vivo. Atorvastatin treatment of diabetic rats leads also to a reduction of NF-κB expression and ERK1/2 phosphorylation. This is in agreement with others who showed that statins reduces NF-κB under normoglycemic conditions in animal models of left ventricular hypertrophy and myocardial infarction as well as in cell culture [64]. Despite extensive research on molecular mechanisms of statins, little is known about the interactions of these drugs with intracellular signalling transduction, including MAPKs. On the other hand, fluvastatin treatment (6 mg/kg) of hypercholesterolemic rats reduced the number of leukocytes that adhered to postcapillary venules in response to platelet activating factor or leukotriene B4 [65] and rosuvastatin (0.5–1.25 mg/kg) attenuates thrombin induced leukocyte rolling, adhesion and transmigration [66].

Table 1: Pharmacodynamic and chemical Characteristics of statins [16]

	Atorvastatin	*Lovastatin*	*Pravastatin*	*Simvastatin*	*Fluvastatin*	*Rosuvastatin*
Dose range (mg/dL)	10-80	10-80	10-80	10-80	20-80	5-40
Maximal LDL-C reduction (%)	60	40	34	47	24	55
Serum triglyceride reduction (%)	29	16	24	18	10	43
Serum HDL-C increased (%)	6	8.6	12	12	8	9,2
Penetration to CNS	No	Yes	No	Yes	No	No
Renal excretion (%)	2	10	20	13	<6	10
Mechanism of hepatic metabolism	Cytochrome p-450 3A4	Cytochrome p-450 3A4	Sulfation	Cytochrome p-450 3A4	Cytochrome p-450 2C9	Cytochrome p-450 2C9
Hydro/lipophilic properties	lipophilic	Lipophilic	hydrophilic	lipophilic	lipophilic	Hydrophilic

Atorvastatin has earlier been shown to inhibit edema formation, neutrophil influx, releaseof his-tamine and inflammatory cytokines and to ameliorate pathological changes in arthritic joints [67,68-70]. Statins, other than atorvastatin, have also been shown to be effective in reducing the disease severity, levels of cytokines and chemokines and inhibiting bone destruction [71-73]. The beneficial effects of statins in arthritis could be attributed to their ability to inhibit HMG-CoA reductase enzyme. By inhibiting this enzyme, statins not only inhibit cholesterol synthesis but also inhibit the synthesis of isoprenoid intermediates that control various inflammatory pathways [74].

Ameliorative Effect of Statin on Diabetic Complications

Statins have been shown to affect the expression, secretion and function of a variety of immune mediators, resulting in the modulation of both adaptive and innate immune functions. Therefore, statins have been considered as a treatment for various inflammatory diseases. A single epidemiological study addressing the relationship between neuropathy and statin therapy suggests a protective effect of both statin and fibrate use against the development of diabetic peripheral sensory neuropathy [75]. The effects of statin therapy on diabetic neuropathy are based mainly on limited animal data. Rosuvastatin treatment has shown to improved nerve conduction velocities and hypoalgesic response to thermal stimulus possibly via decreasing superoxide and nitrotyrosine levels and also decreasing free fatty acids in zucker rats with metabolic syndrome. [76]. Rosuvastatin has shown to improve the recovery of sciatic nerve function and vasa nervorum through increase of neuronal nitric oxide synthase expression. Since, co administration of a specific nitric oxide synthase inhibitor with rosuvastatin attenuated the beneficial effects of rosuvastatin, but these observed effect are independent of lipid lowering effect [77] . In vitro expression studies demonstrated that rosuvastatin inhibited down-regulation of neuronal nitric oxide synthase and restored Akt phosphorylation in Schwann cells . Statins have also been demonstrated to promote the neovascularization of ischemic tissue in normocholesterolemic animals by increasing further functional activity of endothelial progenitor cells [78]. However, diabetic angiopathy that can be in both micro-vessel (such as vasonervorum) and macro-vessels (small-middle diameter arteriesand arterioles), can result in an impairment of tissue functions by leading to ischemia [79,80]. Statins, in this case, may be effective for the prevention of development of diabetic foot ulceration (DFU) as well as for the treatment of DFU via increased oxygenation and nourishment of tissues by increasing perfusion.

CONCLUSION

Statins have the same mode of action via inhibition of HMG-CoA reductase activity but differ between each other in the extent of this inhibition, which leads to different levels of LDL cholesterol lowering. Due to this fact, not only cholesterol synthesis inhibited is but also formation of inflammatory proteins, substances associated with smooth muscle cells proliferation and endogenous synthesis of coenzyme Q10. As the list of pleiotropic effects effects of statins is expanding rapidly, it will become essential to establish their relative biological significance and clinical relevance. LDL cholesterol indubitably represents a modifiable key risk factor for atherosclerosis, and lowering LDL-C blood levels certainly diminishes cardiovascular risk in the long term. The current flurry of interest in the socalled pleiotropic effects of statins should in no way deter practitioners from aggressive management of dyslipidemia, a long established risk factor, as mandated by current guidelines. Nevertheless, it will be important to take action on the new indications which have emerged from consideration of possible pleiotropic effects. Further study of pleiotropic functions of statins may provide insights into the biology of atherosclerosis and other diseases including osteoporosis, rheumatoid arthritis, connective tissue diseases, etc. that could yield benefits in terms of targeting and developing novel strategies

REFERENCE

1. Schachter, M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19:117–25.
2. Schonbeck, U., Libby, P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents Circulation. 2004;109:18–26.
3. Liao, J.K., Laufs, U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005;45:89–118.
4. Kirsch, C., Eckert, G.P., Koudinov, A.R., Muller, W.E. Brain cholesterol, statins and Alzheimer's disease. Pharmacopsychiatry. 2003;36 (Suppl 2): S113-S119.
5. Mackay, D.J., Hall, A. Rho GTPases. J Biol Chem. 1998;273:20685.
6. Nissen, S.E., Tuzcu, E.M., Schoenhagen, P., Crowe, T., Sasiela, W.J., Tsai, J. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352: 29-38.
7. Puddu, P., Puddu, G.M., Muscari, A. HMG-CoA reductase inhibi-tors: Is the endothelium the main target? Cardiology. 2001;95: 9-13.
8. Kleemann, R., Princen, H.M., Emeis, J.J., Jukema, J.W., Fontijn, R.D., Horrevoets, A.J. Rosuvastatin reduces atheroscle-rosis development beyond and independent of its plasma cholesterol-lowering effect in APOE 3-Leiden transgenic mice: evidence for antiinflammatory effects of rosuvastatin. Circulation. 2003;108: 1368-1374.
9. Degraeve, F., Bolla, M., Blaie, S., Creminon, C., Quere, I., Boquet, P. Modulation of COX-2 expression by statins in human aortic smooth muscle cells. Involvement of geranylgerany-lated proteins. J Biol Chem. 2001;276: 46849-46855.
10. Rikitake, Y., Kawashima, S., Takeshita, S., Yamashita, T., Azumi, H., Yasuhara, M. Anti-oxidative properties of fluvastatin, an HMG-CoA reductase inhibitor, contribute to prevention of atherosclerosis in cholesterol-fed rabbits. Atherosclerosis. 2001;154: 87-96.
11. Kuipers, H.F., Rappert, A.A., Mommaas, A.M., van Haastert, E.S., van der Valk, P., Boddeke, H.W. Simvastatin affects cell motility and actin cytoskeleton distribution of microglia. Glia. 2006;53:115.
12. Gotto Jr, A.M., Grundy, S.M. Lowering LDL cholesterol: questions from re-cent meta-analyses and subset analyses of clinical trial data issues from the Interdisciplinary Council on Reducing the Risk for Coronary Heart Disease, ninth council meeting. Circulation. 1999;99: E1e7.
13. Maron, D.J., Fazio, S., Linton, M.F. Current perspectives on statins. Circula-tion. 2000;101:207.
14. Pedersen, T.R. Statin trials and goals of cholesterol-lowering therapy after AMI. Am Heart J. 1999;138:S177e82.
15. van der Most, P.J., Dolga, A.M., Nijholt, I.M., Luiten, P.G., Eisel, U.L. Statins: mechanisms of neuroprotection. Prog Neurobiol. 2009;88:64–75.
16. Daniel Pella., Rafael Raybar & Viola Mechirova. Pleiotropic effect of statin Acta cardiol sin,2005; 21:190-8
17. Qian Zhou.,James K.Liao. pleiotropic effects of statin basic research & clinical prospective circ J 2010; 74: 818-826.
18. Hausding, M., Witteck, A., Rodriguez-Pascual, F., von Eichel- Streiber, C., Forstermann, U., Kleinert, H. Inhibition of small G proteins of the rho family by statins or clostridiumdifficile toxin B enhances cytokine-mediated induction of NO synthase II. Br J Pharmacol. 2000;131:553–61.
19. Danesh, F.R., Kanwar, Y.S. Modulatory effects of HMG-CoA reductase inhibitors in diabetic microangiopathy. FASEB J. 2004;18: 805– 815.
20. Eto, M., Kozai, T., Cosentino, F., Joch, H., Luscher, T.F. Statin prevents tissue factor expression in human endothelial cells: role of Rho/Rho-kinase and Akt pathways. Circulation. 2002;105:1756–9.
21. Masamura, K., Oida, K., Kanehara, H., Suzuki, J., Horie, S., Ishii, H. Pitavastatin-induced thrombomodulin expression by endothelial cells acts via inhibition of small G proteins of the Rho family. Arterioscler Thromb Vasc Biol. 2003;23:512–7.
22. Bellosta, S., Via, D, Canavesi, M., Pfister, P., Fumagalli, R., Paoletti, R., Bernini, F. HMG-CoA reductase inhibitors reduce MMP-9 secretion by macrophages. Arterioscler Thromb Vasc. Biol. 1998;18:1671– 1678.
23. Ikeda, U., Shimpo, M., Ohki, R., Inaba, H., Takahashi, M., Yamamoto, K., Shimada, K. Fluvastatin inhibits matrix metalloproteinase-1 expres-sion in human vascular endothelial cells. Hypertension. 2000;36: 325–329.
24. Giroux, L.M., Davignon, J., Naruszewicz, M. Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocyte-derived macrophages. Biochim Biophys Acta. 1993;1165:335–338.
25. Aviram, M., Hussein, O., Rosenblat, M., Schlezinger, S., Hayek, T., Keidar, S. Interactions of platelets, macrophages, and lipoproteins in hyper-cholesterolemia: antiatherogenic effects of HMG-CoA reductase inhibitor therapy. J Cardiovasc Pharmacol. 1998; 31:39–45.
26. Suzumura, K., Yasuhara, M., Tanaka, K., Suzuki, T.: Protective effect of fluvastatin sodium (XU-62-320), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, on oxidative modifi-cation of human low-density lipoprotein in vitro. Biochem Pharma-col. 1999;57:697–703.
27. Laufs, U., La Fata, V., Plutzky, J., Liao, J.K. Upregulation of endothelial nitric oxide synthase by HMG-CoA reductase inhibitors. Circulation. 1998;97:1129– 1135.
28. O'Driscoll, G., Green, D., Taylor, R.R: Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. Circulation. 1997;95:1126–1131.
29. Endres, M., Laufs, U., Huang, Z., Nakamura, T., Huang, P., Moskowitz, M.A., Liao, J.K. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. Proc Natl Acad Sci USA. 1998; 95:8880–8885.
30. Neuhaus, O., Strasser-Fuchs, S., Fazekas, F., Kieseier, B.C., Niederwieser, G., Hartung, H.P. Statins as immunomodulators: comparison with inter-feron-beta 1b in MS. Neurology. 2002;59:990.
31. Kawakami, A., Tanaka, A., Nakajima, K., Shimokado, K., Yoshida, M. Atorvastatin attenuates remnant lipoprotein-induced monocyte adhesion to vascular endothelium under flow conditions. Circ Res. 2002;91:263.
32. Chung, H.K., Lee, I.K., Kang, H., Suh, J.M., Kim, H., Park, K.C. Statin inhibits interferon-gamma-induced expression of intercellular adhesion molecule-1 (ICAM-1) in vascular endothelial and smooth muscle cells. Exp Mol Med. 2002;34:451.
33. Zapolska-Downar, D., Siennicka, A., Kaczmarczyk, M., Kolodziej, B., Naruszewicz, M. Simvastatin modulates TNFalpha-induced adhesion molecules expression in human endothelial cells. Life Sci. 2004;75: 1287.

34. *Townsend, K.P., Shytle, D.R., Bai, Y., San, N., Zeng, J., Freeman, M. Lov-astatin modulation of microglial activation via suppression of functional CD40 expression. J Neurosci Res. 2004;78:167.*
35. *Rosenson, R.S., Tangney, C.C., Casey, L.C. Inhibition of proinflammatory cy-tokine production by pravastatin. Lancet. 1999;353:983.*
36. *Pahan, K., Sheikh, F.G., Namboodiri, A.M., Singh, I. Lovastatin and phenyl-acetate inhibit the induction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia, and macrophages. J Clin Invest. 1997;100:2671. Patients with diabetic neuropathy treated with sorbinil. NEnglJMed. 319(9), 548−555.*
37. *Rezaie-Majd, A., Maca, T., Bucek, R.A., Valent, P., Muller, M.R., Husslein, P. Simvastatin reduces expression of cytokines interleukin-6, interleu-kin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. Arterioscler Thromb Vasc Biol. 2002;22:1194.*
38. *Romano, M., Diomede, L., Sironi, M., Massimiliano, L., Sottocorno, M., Polentarutti, N. Inhibition of monocyte chemotactic protein-1 synthesis by statins. Lab Invest. 2000;80:1095.*
39. *Grip, O., Janciauskiene, S., Lindgren, S. Pravastatin down-regulates inflammatory mediators in human monocytes in vitro. Eur J Pharmacol. 2000;410:83.*
40. *Waehre, T., Damas, J.K., Gullestad, L., Holm, A.M., Pedersen, T.R., Arnesen, K.E. Hydroxymethylglutaryl coenzyme a reductase inhib-itors down-regulate chemokines and chemokine receptors in patients with coronary artery disease. J Am Coll Cardiol. 2003;41:1460.*
41. *Kobashigawa, J.A., Katznelson, S., Laks, H., Johnson, J.A., Yeatman, L., Wang, X.M., Chia, D., Terasaki, P.I., Sabad, A., Cogert, G.A., Trosian, K., Hamilton, M.A., Moriguchi, J.D., Kawata, N., Hage, A., Drinkwater, D.C., Stevenson, L.W.: Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med. 1995, 333:621–627.*
42. *Kumar, V.L., Guruprasad, B., Wahane, V.D. Atorvastatin exhibits anti-inflammatory and anti-oxidant properties in adjuvant-induced monoarthritis. Inflammopharmacol-ogy. 2010;18:303–8.*
43. *Wahane, V.D., Kumar, V.L. Atorvastatin ameliorates inflammatory hyperalgesia in rat model of monoarticular arthritis. Pharmacol Res. 2010;61:329–33.*
44. *Kwak, B. Statins as a newly recognized type of immunomodulator. Nat. Med. 2004;6: 1399–1402.*
45. *Youssef, S., Stuve, O., Patarroyo, J.C., Ruiz, P.J., Radosevich, J.L., Hur, E.M. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune dis-ease. Nature. 2002;420:78.*
46. *Lawman, S., Mauri, C., Jury, E.C, Cook, H.T., Ehrenstein, M.R. Atorvastatin inhibits autoreactive B cell activation and delays lupus development in New Zealand black/white F1 mice. J Immunol. 2004;173:7641–6.*
47. *Kuipers, H.F., van den Elsen, P.J. Statins and control ofMHC2TAgene tran-scription. Nat Med. 2005;11:365*
48. *Abud-Mendoza, C., de la Fuente, H., Cuevas-Orta, E., Baranda, L., Cruz-Rizo, J., Gonza´lez-Amaro, R. Therapy with statins in patients with refractory rheumatic diseases: a preliminary study. Lupus. 2003; 12:607–11.*
49. *Kanda, H., Yokota, K., Kohno, C. Effects of low-dosage sim-vastatin on rheumatoid arthritis through reduction of Th1/Th2 and CD4/CD8 ratios. Mod Rheumatol. 2007;17:364–8.*
50. *Mc. Carey, D.W., McInnes, I.B., Madhok, R., Hampson, R., Scherbakov, O., Ford, I., Capell, H.A., Sattar, N. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363:2015–21.*
51. *Ghittoni, R., Patrussi, L., Pirozzi, K., Pellegrini, M., Lazzerini, P.E., Capecchi, P. Simvastatin inhibits T-cell activation by selectively impairing the function of Ras superfamily GTPases. FASEB J. 2005;19:605–7.*
52. *Woo, J.T., Nakagawa, H., Krecic, A.M., Nagai, K., Hamilton, A.D., Sebti, S.M. Inhibitory effects of mevastatin and a geranylgeranyl transferase I inhibitor (GGTI-2166) on mono-nuclear osteoclast formation induced by receptor activator of NF kappa B ligand (RANKL) or tumor necrosis factor-alpha (TNF-alpha). Biochem Pharmacol. 2005;69:87–95.*
53. *Ichiki T, Takeda K, Tokunou T.: Dowregulation of angioten- 1998 sin II type 1 receptor by hydrophobic 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors in vascular smooth muscle cells. glutaryl coenzyme A reductase.Arterioscler Thromb Vasc Biol. 2001; 21:1712–1719.*
54. *Sparrow, C.P., Burton, C.A., Hernandez, M., Mundt, S., Hassing, H., Patel. Simvastatin has anti-inflammatory and antiather-osclerotic activities independent of plasma cholesterol lowering. Arterioscler Thromb Vasc Biol. 2001;21:115–21.*
55. *Greenwood, J., Walters, C.E., Pryce, G., Kanuga, N., Beraud, E., Baker, D. Lovastatin inhibits brain endothelial cell Rho-mediated lymphocyte migration and attenuates experimental autoimmune encephalomyelitis. FASEB J. 2003;17:905–7.*
56. *Willerson, J.T., Ridker, P.M. Inflammation as a cardiovascular risk factor. Circulation. 2004;109, II2–II10.*
57. *Xenos, E.S., Stevens, S.L., Freeman, M.B., Cassada, D.C., Goldman, M.H. Nitric oxide mediates the effect of fluvastatin on intercellular adhesion molecule-1 and platelet endothelial cell adhesion molecule-1 expression on human endothelial cells. Ann. Vasc. Surg. 2005;19, 386–392.*
58. *Irani, K. Oxidant signaling in vascular cell growth, death, and survival: a review of the roles of reactive oxygen species in smooth muscle and endothelial cell mitogenic and apoptotic signaling. Circ. Res. 2000;87: 179–183*
59. *Hawiger, J. Innate immunity and inflammation: a transcriptional paradigm. Immunol. Res. 2001;23: 99–109.*
60. *Tschope, C., Walther, T., Escher, F., Spillmann, F., Du, J., Altmann, C., Schimke, I., Bader, M., Sanchez-Ferrer, C.F., Schultheiss, H.P., Noutsias, M. Transgenic activation of the kallikrein–kinin system inhibits intramyocardial inflammation, endothelial dysfunction, and oxidative stress in experimental diabetic cardiomyopathy. FASEB J. 2005;19, 2057–2059.*
61. *Riad, A., Westermann, D., Stephan B.F., Heinz P.S., Carsten, T. Atorvastatin led under severe diabetic conditions to anti-oxidative and anti-inflammatory. J Clinic Experiment Cardiol. 2007; 1: 1-5.*
62. *Delbosc, S., Morena, M., Djouad, F., Ledoucen, C., Descomps, B., Cristol, J.P. Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are able to reduce superoxide anion production by NADPH oxidase in THP-1-derived monocytes. J Cardiovasc Pharmacol. 2000;40:611–617.*

63. *Rueckschloss, U., Galle, J., Holtz, J., Zerkowski, H.R., Morawietz, H. Induction of NAD(P)H oxidase by oxidized low-density lipoprotein in human endothelial cells: antioxidative potential of hydroxymethylglutaryl coenzyme A reductase inhibitor therapy. Circulation 104. 2001;1767–1772.*
64. *Wang, Y., Schmeichel, A. M., Iida, H., Schmelzer, J. D., & Low, P. A. Enhanced inflammatory response via activation of NF-kappaB in acute experimental diabetic neuropathy subjected to ischemia–reperfusion injury.J Neurol Sci 247. 2006;(1), 47−52.*
65. *Kimura, M., Kurose, I., Russell, J., Granger, D.N. Effects of fluvastatin on leukocyte-endothelial cell adhesion in hyperch-olesterolemic rats. Arterioscler Thromb Vasc Biol. 1997;17: 1521–6.*
66. *Stalker, T.J., Lefer, A.M., Scalia, R. A new HMG-CoA reductase inhibitor, rosuvastatin, exerts anti-inflammatory effects on the microvascular endothelium: the role of mevalonic acid. Br J Pharmacol. 2001;133:406–12.*
67. *Barsante, M.M., Roffê, E., Yokoro, C.M., Tafuri, W.L., Souza, D.G, Pinho, V. Anti-inflammatory and analgesic effects of atorvastatin in a rat model of adjuvant-induced arthritis. Eur J Pharmacol. 2005;516:282–9.*
68. *Majlesi, Y., Samorapoompichit, P., Hauswirth, A.W., Schernthaner, G.H., Ghannadan, M., Baghestanian, M. Cerivastatin and atorvastatin inhibit IL-3-dependent differentiation and IgE-mediated histamine release in human basophils and downmodulate expression of the basophil-activation antigen CD203c/E-NPP3. J Leukoc Biol. 2003;73:107–17.*
69. *Hernández-Presa, M.A., Martín-Ventura, J.L., Ortego, M., Gómez-Hernández, A., Tuñón, J., Hernández-Vargas, P. Atorvastatin reduces the expression of cyclooxygenase-2 in a rabbit model of atherosclerosis and in cultured vascular smooth muscle cells. Atherosclerosis. 2002;160:49–58.*
70. *Yokota, K., Miyazaki, T., Hirano, M., Akiyama, Y., Mimura, T. Simvastatin inhibits production of interleukin 6 (IL-6) and IL-8 and cell proliferation induced by tumor necrosis factor-alpha in fibroblast-like synoviocytes from patients with rheumatoid arthritis. J Rheumatol. 2006;33:463–71.*
71. *Leung, B.P., Sattar, N., Crilly, A., Prach, M., McCarey, D.W., Payne, H. A novel anti-inflammatory role for simvastatin in inflammatory arthritis. J Immunol. 2003;170:1524–30.*
72. *Funk, J.L., Chen, J., Downey, K.J., Clark, R.A. Bone protective effect of simvastatin in experimental arthritis. J Rheumatol. 2008;35:1083–91.*
73. *Yamagata, T., Kinoshita, K., Nozaki, Y., Sugiyama, M., Ikoma, S., Funauchi, M. Effects of pravastatin in murine collagen-induced arthritis. Rheumatol Int. 2007;27:631–9.*
74. *Zhao, D., Pothoulakis, C. Rho GTPases as therapeutic targets for the treatment of inflammatory diseases. Expert Opin Ther Targets. 2003;7:583–92.*
75. *Davis, T.M., Yeap, B.B., Davis, W.A., Bruce, D.G. Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. Diabetologia. 2008;51:562–6.*
76. *Oltman, C.L., Davidson E.P., Coppey, L.J. Attenuation of vascular/neural dysfunction in Zucker rats treated with enalapril or Rosuvastatin. Obesity (Silver Spring)16. 2008;82–89.*
77. *Li, F., Drel, V. R., Szabo, C., Stevens, M. J., & Obrosova, I. G. Low-dose poly(ADP-ribose) polymerase inhibitor-containing combination therapies reverse early peripheral diabetic neuropathy.Diabetes. 2005;54(5), 1514−1522.*
78. *Vasa, M., Fichtlscherer, S., Adler, K. Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease. Circulation. 2001;103:2885–90.*
79. *Klein, R., Klein, B.E., Moss, S.E., Cruickshanks K.J. Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. Arch Intern Med. 1994;154(19): 2169–78.*
80. *Schalkwijk, C.G., Stehouwer, C.D. Vascular complications indiabetes mellitus: the role of endothelial dysfunction. Clin Sci. 2005;109:143–59.*