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REVIEW ARTICLE

Statins: Newer Roles Including Lipid Lowering Therapy

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ABSTRACT

Statins are most effective pharmacological agents to decrease total plasma cholesterol level by competitive inhibition of hydroxyl methyl glutaryl Coenzyme A (HMG-CoA) reductase. Apart from the well-known Low density lipoprotein (LDL)-and cholesterol-lowering effect, statins have been postulated to exert other beneficial effects called pleotropic effects. Better understanding of various pleotropic effects of statins has prompted a new surge of interest in their use to treat or prevent a wide range of chronic and life-threatening disorders. Their effectiveness in treating these disorders suggests that the benefits of statins may not be limited to its cholesterol-lowering effect. Although the clinical implication of this beneficial non-lipid effect seems promising, yet properly-designed, large multicentre, prospective, control trials are needed to validate the use of statins for indication other than primary and secondary prevention of vascular disease.

Keywords: *Statins, Hydroxyl methyl glutaryl Coenzyme A (HMG-Co A) reductase, Pleotropic effect, Lipid-lowering drug*

Statins are structurally similar to hydroxyl methyl glutaryl Coenzyme A (HMG-CoA), a precursor of cholesterol HMG-CoA reductase which regulates the rate-limiting step in the synthesis of cholesterol. They are most efficient agent for reducing plasma cholesterol by competitively-inhibiting the principle enzyme involved [1]. Regulation of plasma cholesterol lowers the risk of cardiovascular events in both primary and secondary preventions levels. Mevallonic acid, the product of HMG-CoA reductase is not only the substrate for cholesterol synthesis but it is also the precursor of isoprenoids and other metabolites involved in different cellular pathway of atherogenesis and thrombosis [2]. As a consequence, statins have the potential to elicit in pleotropic effect, which are independent of cholesterol reduction and may explain many of the direct anti-atherosclerotic and anti-thrombotic properties of these compounds. They are involved in maintenance of endothelial function, increased tissue antioxidant capacity, and inhibition of smooth muscle cells proliferation and inflammation, increased stability of atherosclerotic plaques, restoration of platelet activity and coagulation process. Statins also inhibit tumor cell growth and enhance intracellular calcium mobilation. Recently, it was reported that satins have anti-inflammatory and immunomodulatory role and may be relevant for treatment of atherosclorosis. Statins are classified in various ways on the basis of their sources, metabolic pathways, physiochemical properties and specific activity [3, 4].

MECHANISMS FOR THE ACTION OF STATINS

(i) Mechanisms involving lipids

Statins target hepatocytes and inhibit HMG-CoA reductase, the enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor. The statins not only compete with the normal substrate in the enzymes active site but also alter the conformation of the enzyme when they bind to its active site and prevent HMG-CoA reductase from attaining a functional structure. The change in conformation at the active site makes these drugs very effective and specific. Binding of statins to HMG-CoA reductase is reversible, and their affinity for the enzyme is in the nanomolar range, as compared to the natural substrate that has micromolar affinity [5]. The inhibition of HMG-CoA reductase determines the reduction of intracellular cholesterol by inducing the activation of protease, which sequentially cleaves the

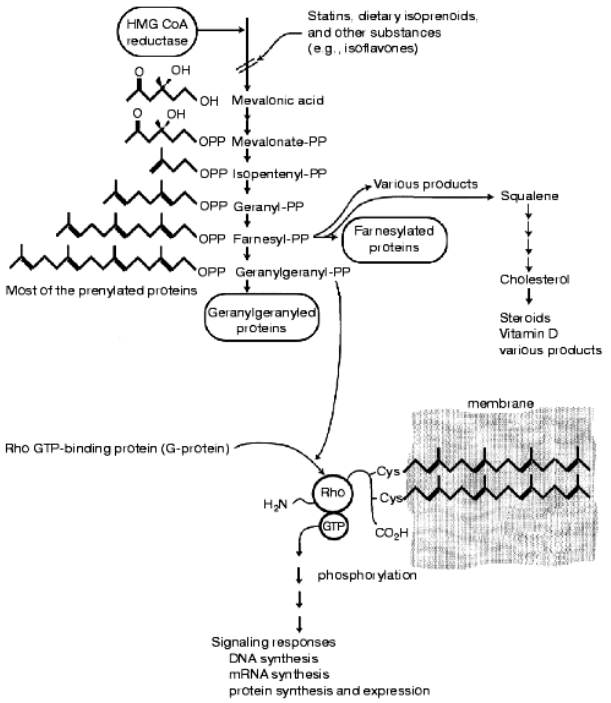

Fig 1. Generalized scheme depicting isoprenoid metabolism to a geranylgeranyl-conjugated Rho GTP-binding in cellular signal transduction. Both mevalonic acid and geranylgeranyl-PP are reported to compensate for statin effects on cells, whereas cholesterol is non-compensatory (see text).

sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. SREBPs are translocated at the level of the nucleus, where they increase the gene expression for LDL receptor. The reduction of cholesterol in hepatocytes leads to the increase of hepatic LDL receptor that determines the reduction of circulating LDL and of its precursors (intermediate density - IDL and very low density-VLDL lipoproteins) [6]. Statins inhibit hepatic synthesis of apolipoprotein B-100, determining a reduction of the synthesis and secretion of triglyceride-rich lipoproteins [7].

(ii) Mechanisms involving intracellular signaling pathways (non-lipid pleotropic effect)

As shown in Fig 1, a variety of proteins have covalently attached isoprenoid groups, mainly the C15 farnesyl and C20 geranylgeranyl residues. Many prenylated proteins are associated with intracellular membranes and mutating their Cys prenylation sites blocks their membrane localization. The hydrophobic prenyl group can act to anchor its attached protein to a membrane. Prenylated proteins may interact with specific membrane - bound receptor proteins and hence prenylation also mediates protein – protein interactions [8].

The complex process of cell signaling is very important for intercellular communication. Extracellular signaling molecules, which are water-soluble and have high molecular weight, need to bind to specific receptors on the cell surface, which transduce the extracellular signals into the cell by intracellular signaling pathways (cascades). Many intracellular signaling molecules are prenylated proteins. The specific receptors on the cell surface are associated with trimeric G protein, or have Ser/Thr/Tyr kinases activities. The trimeric G protein has a geranylgeranylated subunit (gamma), allowing this signaling protein to be inserted in the cell membrane near specific membrane receptors and to receive extracellular signals, which are then transferred to the secondary signaling molecules in the cell. Another important class of prenylated signaling molecules is the components of Ras family, which are farnesylated and intermediate the Ser/Thr/Tyr kinases activities of membrane receptors from the cell surface.

The mevalonate pathway yields a series of isoprenoids, which are vital for diverse cellular functions. These isoprenoids include: isopentenyl adenosine, present in some types of transfer RNA, dolichols required for glycoprotein synthesis, and poly-isoprenoid side chains of ubiquinone and hemeA, involved in electron transport [9].

ROLES OF STATINS

(i) Pleotropic effect and cardiovascular effects

Due to the non lipid-pleotropic effects, statins have wide range of applicability in different therapies which are as follows (Table 1) [10];

1. Statins as anti-inflammatory drugs and immunomodulatory drugs

Statins may interfere directly with several key mechanisms of the inflammatory response in all the steps of atherogenesis involving different cellular elements like: endothelial cells (ECs), smooth muscle cells (SMCs), macrophages, and lymphocytes [11].

a. Statins modulate the fuction of monocytes i.e.chemotaxis

The early step in atherogenesis involves monocyte adhesion to the endothelium that owing to various stimuli (turbulence, dyslipidemia, toxins, and so forth) acquires activated phenotype. The interaction of the monocytic surface receptor with activated endothelium provides adhesion and migration of monocytes across it. Monocytes that infiltrate this lesion generate chemotactic stimuli and attract other leukocytes to the same site, provocate inflammatory reaction through all phases of atheroma development. The spectrum of immunomodulatory properties of these drugs related to monocyte function includes effect on expression of surface proteins and adhesiveness, adhesive interaction between monocytes and vascular wall, and proliferation and differentiation.

The mechanism that is responsible for the increased adhesion of monocytes in patients with hypercholesterolemia has been attributed to abnormal monocyte function with respect to eicosanoid metabolism and superoxide anion production [12]. Certain statins, *i e*. lovastatin [13], pravastatin [14],

simvastatin [15] have an inhibitory effect on superoxide anion formation and subsequent LDL oxidation in activated monocytes [16]. The influence of statins on the differentiation of monocytes was shown by Weber *et al* in 1995 [17]. They reported that lovastatin increased surface protein expression of CD14 and CD11b in human monocytic Mono Mac 6 cells, enhanced adhesiveness to human umbilical vein endothelial cells and retarded the growth and proliferation.

b. Statin preserve the endothelial function

Endothelial dysfunction represents an early event in the initiation of atherosclerotic lesion, induced by hypercholesterolemia. Nitric oxide (NO) regulates the anti-atherosclerotic function of the endothelium [18]. Hypercholesterolemia reduces the capacity of endothelial cells to produce NO, probably due to the reduced availability of L-arginine, the physiologic substrate of NO synthase, and determines an increased degradation of NO. Cholesterol reduction by statins leads to a significant increase of the endothelial function. The effect of statins on the endothelial function can be partially independent of the reduction of the lipid level. Simvastatin, as well as lovastatin, induce the transcriptional activation of eNOS gene in human endothelial cells *in vitro* [19]. Activation of eNOS by statins takes place post-translationally and is prevented by isoprenoid derivatives, mevalonate and geranylgeraniol. The endothelial function was increased in primates treated with pravastatin, without the reduction of LDL cholesterol.

c. Impact of statins on vascular smooth muscle cells (SMCs) and plaque stability.

The accumulation of SMCs in the intima is an early feature of atherosclerosis that results from a combination of migration from the media, proliferation and eventual death, including apoptosis. The data regarding the influence of statins on these processes, and collagen production by SMCs are much more controversial. First and foremost, it has been proved that HMG-CoA reductase inhibitors may alter SMCs proliferation and migration [20-22], although their effects were distinct and associated with hydrophilic-lipophilic properties. There is evidence of decreased *in vitro* SMCs proliferation after exposure to serum from patients treated with lipophilic statin–fluvastatin, but not with hydrophilic paravastatin.

The ability of statins to suppress the increased oxidative stress and related SMCs migration has been considered an additional basis for anti-atherosclerotic therapy. Indeed, lipophilic compounds such as simvastatin and fluvastatin exhibited greatest impact on SMC oxidative stress and migration than hydrophilic pravastatin did.

d. The suppression effect of statins on different T-cell function

T-cells are prominent components of both early and late atherosclerotic lesions and the role of Th1/Th2 cells subsets in the evolution and rupture of the plaque is currently under investigation. Suppression of lymphoid cell function *in vitro* such as proliferation or natural killer cell activity by compactin, lovastatin and simvastatin has been reported [23-25].

e. Effect of statins on macrophages

The other important cells accumulating in atherosclerotic plaque are macrophages that are involved in all the phases of atherosclerosis from initiation through progression and finally plaque rupture and thrombosis. Several works have demonstrated that macrophages proliferate in human and hypercholesterolemic rabbit atheroma [26]. Survival factors such as macrophage-colony stimulating factor (M-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) induce macrophage proliferation *in vitro* [27, 28] and ox-LDL enhances their action [29]. This macrophage proliferation may contribute to formation of the macrophage rich vulnerable atheroma.

2. Statins as antioxidant

At least 4 mechanisms were proposed to explain statins antioxidant properties [30].

(a) The hypocholesterolemic effect, resulting in reduced lipoprotein cholesterol, and thus, reduced level of oxidation substrate;

(b) The decrease of cell oxygen production, by inhibiting the generation of superoxide by macrophages. Recently, it was demonstrated that statins could attenuate the formation of superoxide anion in endothelial cells, by preventing the prenylation of p21 Rac protein [31]. Statins can also prevent LDL oxidation by preserving the activity of the endogenous antioxidant system, like superoxide dismutase [32].

(c) The binding of statins to phospholipids on the surface of lipoproteins (fluvastatin and lovastatin bind to LDL phospholipids) preventing the diffusion towards the lipoprotein core of free radicals generated during oxidative stress;

(d) The potent antioxidative potential of the statin metabolites (i.e. atorvastatin and fluvastatin metabolites) also results in protection of lipoproteins from oxidation [33].

3. Statins as antithrombotic agent (Fig 2)

a. Effects on the stability of the atherosclerotic plaque

Coronary events are the result of unstable atherosclerotic lesion rupture and thrombus formation [34]. The plaque instability, manifested as an ulceration of the fibrous cap, the rupture of the plaque and internal hemorrhage, are characteristics of the plaques with numerous lipid deposits and macrophages in the cap. Recently, it was demonstrated that statins (fluvastatin, simvastatin) can inhibit the gelatinolytic activity of metalloproteases, as well as their secretion by human macrophages in culture [35]. Angiographic studies showed that statins reduce the progression and induce the regression of coronary atherosclerosis, reduce the

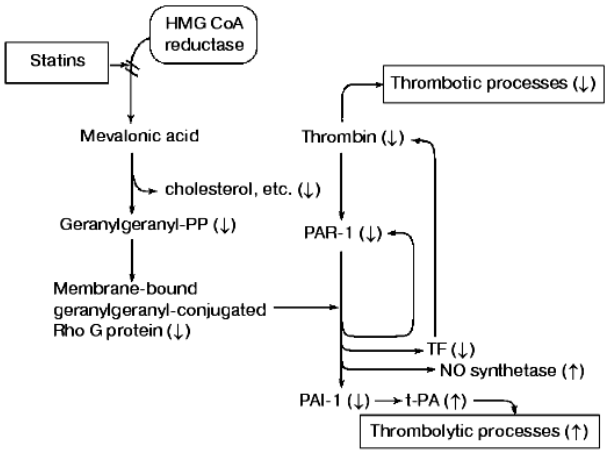

Fig 2. A composite of isoprenoid-conjugated proteins and cellular thrombin generating pathways. The statin-induced shift is shown from favoring thrombotic to thrombolytic processes (Figure courtesy of John W. Fenton, II).

formation of new lesions and the incidence of coronary events [36]. Computer tomography provided evidence of the reduction in the volume of coronary calcified plaques after 12 months of statin treatment. It was concluded that alterations in the composition of lesions confers an increased stability.

b. Effects on platelet activation

Hypercholesterolemia is associated with hypercoagulability, as well as with increased platelet activation. An increased level of LDL determines increased platelets reactivity, associated with an increased thromboxane A2 biosynthesis. Recently, a new mechanism was elucidated where by platelet activity is increased in hypercholesterolemia due to LDL inhibiting the platelet antiport Na^+/H^+ [37]. In addition, platelet dependent thrombin generation is increased in hypercholesterolemic subjects, and pravastatin treatment determines a restoration of thrombin formation. Statin therapy was accompanied by a reduction of platelet aggregation induced by ADP, collagen or fibrinogen, as well as of thromboxane production, in parallel with LDL cholesterol reduction.

c. Effects on the coagulation process

Primary and secondary prevention studies demonstrate that statin therapy reduces significantly thrombus formation. Recently, a link between the enhancement of endothelial fibrinolytic system and the inhibition of mevalonate pathway was reported [38]. The tissue factor plays an important role in the initiation of the extrinsic coagulation pathway and it was localized in lipid-loaded macrophages from atherosclerotic plaque. Recently, Colli et al [39] have shown that lipophilic statins (simvastatin and fluvastatin) reduce the expression and activity of the tissue factor in human monocyte-derived macrophages in culture, effect prevented by the addition of mevalonate and transgeranylgeraniol.

4. Statins as antiarrhythmic therapy

Recently, it has been proposed that statins reduce the incidence of arrhythmias in patients with atherosclerotic heart disease. They reduce the ventricular tachycardia/ ventricular fibrillation (VT/VF) [40]. In addition, lipid-lowering therapy was associated with significant reduction in both cardiac mortality and all-cause death in larger cohort of patients treated with antiarrhythmic drug therapy. Recent study [41] suggests that the anti-inflammatory effect of statins can reduce the recurrence of atrial fibrillation. The beneficial effect of statin therapy in preventing AF may be mediated through its effect on the progression of coronary artery disease CAD [42]. Also, in addition to this indirect antiarrhythmic effect statins may exhibit direct antiarrhythmic effects by modulating the fatty acid composition in physio-chemical properties of cell membranes, with resultant alterations in transmembrane ion channel properties [43, 44]. Moreover statins have multiple pleotropic effects (independent of lipid lowering). They decrease the messenger ribonucleic acid (mRNA) levels for interleukin-8, monocyte, and chemo attractant protein-1, plasminogen activator inhibitor-1 and endothelin-1. They increase the levels of thrombomodulin, an endothelial nitric oxide synthases (eNOS) [45]. Statins also act on G-proteins. This leads to reduced eNOS and mRNA degradation and higher eNOS protein levels and their activity. In addition, by scavenging free radicals and reactive oxygen species statins prevent nitric oxide degradation and preserve endothelial function. All these mechanisms result in improved endothelial function leading to coronary vasodilatation, increased coronary blood flow and less myocardial ischemia with reduced likelihood of AF.

5. Statin and peripheral arterial disease (PAD)

According to a recent randomized, double blind parallel-design study [46], atorvastatin achieved greater improvement in pain-free walking time and participation in physical activity in patient with intermittent claudication than did inactive placebo. The beneficial effects of statin in PAD may be attributed to increased production of nitric oxide in the endothelium, which has local vasodilator propertities in addition to antithrombogenic, antiproliferative, and leukocyte adhesion-inhibiting effect [47, 48]. Other mechanism by which statin favorably influence lower limb ischemia include enhancement of endothelium-dependent relaxation, and inhibition of platelet function [49] and endothelin-1 which is a potent vasoconstrictor and mitogen [50]. Reduction of vascular inflammation may be an additional mechanism by which statin are associated with better functioning in patient with PAD. Statin-associated reduction of inflammatory cytokines could improve blood flow, regress atherosclerosis, or improve end-organ fuction [51].

6. Statin and Non-ischemic cardiomyopathy

The anti-inflammatory properties of statin may confer greater benefit than just reducing the risk of AF.

The result of a recently-published randomized controlled trial by Node et al. [52] suggest that the anti-inflammatory effect of statin result in improved neurohormonal imbalance and cardiac function and may benefits patient with symptomatic non-ischaemic dilated cardiomyopathy. Investigator reported that there were positive correlation between change in ejection fraction and reduction in circulating inflammatory cytokines, suggesting that statin may improve cardiac function in part by modulating the inflammation state.

(ii) Pleotropic effect and other disease state.

1. Statins and Neuro inflammatory Disorders

Statins have beneficial effects in patients with multiple sclerosis. Recent studies indicate that statins have immunomodulatory properties. Statins decrease the migration of leucocytes into the central nervous system, inhibit major histocompatibility complex II and co-stimulatory signals required for activation of proinflammatory cells, induce a TH2 phenotype investigated in T cells and decrease the expression of inflammatory mediators in the central nervous system, including nitric oxide and tumor necrosis factor alpha. These immuno-modulatory effects can either inhibit or reverse chronic and relapsing experimental autoimmune encephalomyelitis, a model of multiple sclerosis [53]. Data from epidemiological trials indicate that statins may have some protective effect against the development of Alzheimer's disease as well.

2. Statins and psychological well being

Two recent studies have associated long-term use of statin with reduced risk of depression in-patient with coronary artery disease [54]. Young and collogues hypothesize that the penetration of the blood brain barrier by the lipophilic statins accounts for most of the observed impact on psychological well being. The investigators observed that use of statin was inversely associated with depression but such an association was not likely to be directly casual because there is no known pharmacological mechanism for this effect. However, they suggested that a possible explanation could be an indirect effect of statins on the risk of depression through improved quality of life due to increased incidence of cardiovascular events or more health consciousness and compliance among patients having longer lipid treatment.

3. Statins and cancer

Statins have been shown to inhibit proliferation and to induce apoptosis in a variety of tumor cells [55-57]. They have also been found to display antitumor effects against melanoma, mammarycarcinoma, pancreaticadenocarcinoma, fibrosarcoma, glioma, neuroblastoma, and lymphoma in animal tumor models resulting in retardation of tumor growth, and/or inhibition of the metastatic process.

The molecular mechanisms underlying antitumor activity statins have not been fully elucidated but interference with the function of Ras and Rho family GTPases, inhibition of the activity of certain cyclic dependent kinases (CDK), and activation of CDK inhibitors, all seem to participate in this activity. The fact that mevalonate plays a key role in cell proliferation and that many malignant cells present an increased HMG-CoA reductase activity, suggests that a selective inhibition of this enzyme could lead to a new chemotherapy for cancer disease. Results obtained i*n vitro* have shown that statins can inhibit tumor cell growth, a fact confirmed by some *in vivo* experiments also. The obtained reduction of sterols synthesis by statins, suggests that inhibition of tumor cell growth can be related to the reduction of nonsteroidal isoprenoid compounds.

Future directions in the development of the statins as an anticancer agents include combinations with chemotherapeutic or other molecular –targeted agents, combinations with radiotherapy, maintenance therapy in minimal disease status, and as chemo preventive therapy.

4. Statins and osteoporosis

Statins have been linked to a reduction in the incidence of fractures in elderly patients [58,59]. After adjusting for multiple factors, such as age, body mass index, and estrogen use among statin users in each of the four prospective studies, a trend toward fewer hip and non-spine fractures was observed. Similar reductions in risk were reported in the Meta analysis of observational studies; statin use was associated with an estimated 57% reduction in hip fracture, and an estimated 31% reduction in non-spine fracture.

Recent experimental evidence supports a role for mevalonate pathway in murine and rabbit osteoclast formation and bone resorption. Lovastatin inhibited both processes. In addition, it was demonstrated *in vitro* and *in vivo* in rodents, that statins enhance new bone formation. Statins administration is associated with a decrease of bone fracture risk in subjects over 50 years, probably because of the increase of the mineral density of the bones. Thus, subjects with hyperlipidemia known to present increased risk for osteoporosis (mostly post-menopausal women) could benefit from statin therapy.

5. Statins and age-related maculopathy

Age-related maculopathy (ARM) is the leading cause of irreversible vision loss among older adults in the western world. Based on the presence of similar risk factors, some suggest that the pathophysiologies of ARM and cardiovascular disease have similar casual pathways and therefore, both groups of patients may benefit from the same drug treatment. Results suggest that statin use is associated with a significant size reduction of ARM [60].

ADVERSE EFFECTS OF STATIN THERAPY

Statins are generally well tolerated. The most important adverse effects are liver and muscle toxicity. Myopathy can happen if inhibitors of cytochrome P450 or other inhibitors of statins metabolism are administered together with statins, which increase blood

concentration of statins. Such are the azole antifungal. Fibrates and niacin enhance myopathy risk of statins by a mechanism not involving the increased statins blood concentration. Other risk factors are hepatic dysfunction, renal insufficiency, hypothyroidism, advanced age and serious infections.

Table 1. Important pleiotropic effects of various statins and cardiovascular implications

Effect	Mechanism of action	Change	Statins	Type of Study	Implications	Reference
Anti- inflammatory effect	C-Reactive Protein	↓	cerivastatin	C	Used in CAD, ACS, PCI	[67]
		↓	Pravastatin	C		[68]
		↓	Fluvastatin	C		[69]
		↓	Fluvastatin	C, E		[70, 71]
	MCP-I	↓	Fluvastatin	I	Prevents chemotaxis	[72]
		↓	Pravastatin	I		[73]
		↓	Lovastatin	I		[74]
	Growth and proliferation of macrophages	↓	Cerivastatin	E, I		[75, 76]
	Apoptosis	↓	Pravastatin	E	Retard hyperplasia and restenosis, thereby produces plaque stability initially	[77]
		↑	Fluvastatin	E		[77]
		↑	Simvastatin	I		[78, 79]
		↑	Lovastatin	I		[79]
		↑	Atorvastain	I		[79]
		↑	Pravastatin	E		[77]
	Collagen gene expression and synthesis of collagen	↓	Pravastatin	E	Plaque stability later	[77]
			Fluvastatin	E		[77]
	m-RNA cyclooxygenase-2	↓	Lovastatin	I	Reduces vascular inflammation	[80]
		↓	Simvastatin	I		[80]
	Monocyte infilteration and V-CAM-1	↓	Cerivastatin	E, I	Prevents chemo taxis	[101, 102]
Immuno-modulatory	T-cell proliferation	↓	Lovastatin	I	Reduces vascular inflammation &anti rejective role & anti proliferative role	[81]
	Expression of MHC II	↓	Simvastatin	I		[82]
		↓	Provastatin	I		[82]
		↓	Atorvastain	I		[83]
	Antigen presenting cell and T-cell activation	↓	Lovastatin	I		[83]
		↓	Pravastatin	I		[83]
		↓	Pravastatin	I		[84]
	TNF-	↓	Pravastatin	I		[84]
	Interleukin –1	↓	Simvastatin	I		[85]
	IL-8	↓	Simvastatin	C		[86]
	IL-6	↓	Lovastatin	I		[80]
	PPAR and	↓	Simvastatin	I		[80]
	Isoprenylation of Ras and Rho genes	↓	Pravastatin	C	Vascular antiproliferation in transport associated artereo sclerosis	[89]
Endothelial dysfunction improvement, increased NO bioavailability	Isoprenylation of Ras and Rho genes	↓	Atorvastain	I, E	Cardiovascular hemostasis vasodialation and anti proliferative	[87, 88]
	Activation of eNOS through proteinkinase	↑	Simvastatin	E		[90]
		↑	Rosuvastatin	E		[64]
	Aortic caveolin-I protein an inhibitor of NOS	↓	Rosuvastatin	E		[63]
Antioxidant action	Bioavailability of NO, which can antagonize vasoconstrictive properties of ROS	↑	Simvastatin	E	Reduces cardiovascular oxidative stress	[91]
	Lipid peroxidation and ROS production	↓	Simvastatin	C		[93]
	Myeloperoxidase derived ROS	↓	Atorvastatin	C		[61]
↓ LDL oxidation	Scavenge superoxide free radical	↑	Fluvastatin	I	Antiatherogenic effect	[66]
		↑	Simvastatin	I		[92]
	NAD (P) H oxidase	↓	Fluvastatin	I		[66]
		↓	Simvastatin	I		[92]
	Inflamation cascade	↓	Fluvastatin	I		[66]
		↓	Simvastatin	I		[92]
Plaque stability	Matrix metalloproteinases (MMP-9)	↑	Cerivastatin	I, E	Useful in ACS, MI, and UA	[62, 94]
		↑	Pravastatin	I		[95]
	Cholestrol ester content	↑	Pravastatin	I		[95]
	Volume of collagen contents	↑	Pravastatin	I		[95]
	Monoocyte infiltaration in artery wall	↑	Atorvastatin	E		[96]
	Apoptosis	↑	Pravastatin	E		[77]
		↑	Fluvastatin	E		[77]
		↑	Simvastatin	I		[78, 79]
		↑	Lovastatin	I		[79]
		↑	Atorvastatin	I		[79]

Favouurable co-agulation	Activation of extrinsic coagulation pathway	↓	Simvastatin	C	Impede Thrombogenesis	[97]
		↓	Fluvastatin	C		[65]
	Platelet adhesion and aggregation	↓	Pravastatin	C		[98]
	Improve rheologic profile	↑	Pravastatin	C		[98]
Normalization of sympathetic out-flow	NO synthesis	↑	Rosuvastatin	E	Useful in Hypertension, MI, Cerebral ischemia and CHF	[64]
		↑	Simvastatin	E		[91]
	Angiotensin-II and AT1 receptor expression	↓	Cerivastatin	C		[99]
	ETA Receptor expression	↓	Atorvastati	I		[100]
		↓	Simvastatin	I		[100]
	Normalization of sympathetic reflux regulation	↑	Simvastatin	E		[91]
Effect in peripheral arterial disease (PAD)	NO synthesis	↑	Simvastatin	E	Improve lower extremity functioning in PAD pa-tients	[91]
	Platlet Function	↓	Atorvastatin	C		[97]
	Endothelin-1	↓	Simvastatin	I		[100]

↑: Increases; ↓: decreases; I: in vitro study; E: experimental study; C: Clinical Trial; ICAM-1: intracellular adhesion, MCP-1: monocyte chemotactic protein-1, PPAR-α or γ: Peroxisome proliferator activated receptor α or γ, CAD: coronary artery disease, ACS: Acute coronary syndrome, PC I: Percutaneous coronary intervention, MI: Myocardial infraction, UA: Unstable Angina, CHF: Congestive heart failure

CONCLUSION

Inhibitors of 3-hydroxy-3-methyl glytaryl coenzyme A reductase or statins are effective lipid-lowering drugs, which are widely used in clinical practice. In recent years, considerable data have accumulated regarding their pleotropic effect particularly as an anti-inflammatory and immunomodulatory therapy. Review of the literature allows us to conclude that statin owing to their influence on cellular metabolism may interfere directly with several key mechanisms for various pharmacological activities. Accumulating knowledge in the action of these drugs may broaden the application of statin to the treatment of non-cardiovascular disease.

REFERENCES

1. Hunninghake DB. HMG-CoA reductase inhibitors. Curr Opin Lipidol 1992; 3: 22-8.
2. Goldstein JL, Brown MS. Regulation of the Mavelonate Pathway. Nature 1990; 343:425-30.
3. Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. Clin Pharmacokinet 1997; 32:403-25.
4. Blumenthal RS. Statins: Effective antiatherosclerotic therapy. Am Heart J 2000; 139: 577- 83.
5. Corsini A, Bellosta S, Baetta R, Fumagalli R, Bernini F. New insights into the pharmacodynamics and pharmacokinetic properties of statins. Pharmacol Ther 1999; 84:413-28.
6. Sehayek E, Butbul E, Avner R. Enhanced cellular metabolism of very low density lipoprotein by simvastatin: a novel mechanism of action of HMG-CoA reductase inhibitors. Eur J Clin Invest 1994; 24:173-8.
7. Ginsberg HN, Le NA, Short MP, Ramakrishnan R, Desnick RJ. Suppression of apolipoprotein B production during treatment of cholesteryl ester storage disease with lovastatin: implication for regulation of apolipoprotein B synthesis. J Clin Invest 1987; 80:1692-7.
8. Voet D, Voet JG. Lipids and membranes. In: John Wiley & Sons, Inc., eds., Biochemistry, Second Edition, USA, 1995, pp. 315-6.
9. Bernini F, Didoni G, Bonfadini G, Bellosta S, Fumagalli R. Requirement for mevalonate in acetylated LDL induction of cholesterol esterification in macrophages. Atherosclerosis 1993; 104:19-26.
10. Tandon V, Bano G, Khajuria V, Parihar A, Gupta S. Pleiotropic effect of statin. Ind J of Pharmacol 2005; 37: 77-85.
11. Nishbori M, Takahashi HK, Mori S. The regulation of ICAM-1 and LFA-1 interaction by autacoids and statins: a novel strategy for controlling inflammation and immune responses. J Pharmacol Sci 2003; 92:7-12.
12. Stragliotto E, Camera M, Postiglione A, Sirtori M, Di Minno G, Tremoli E: Functionally abnormal monocytes in hypercholesterolemia. Arterioscler Thromb 1993; 13:944-50.
13. Aviram M, Dankner G, Cogan U, Hochgraf E, Brook JG. Lovastatin inhibits low-density lipoprotein oxidation and alters its fluidity and uptake by macrophages: in vitro and in vivo studies. Metabolism 1992; 41:229-35.
14. Hoffman R, Brook GJ, Aviram M. Hypolipidemic drugs reduce lipoprotein susceptibility to undergo lipid peroxidation: in vitro and in vivo studies. Atherosclerosis 1992; 93:105-13.
15. Giroux LM, Davignon J, Naruszewicz M. Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocyte-derived macrophages. Biochim Biophys Acta 1993; 1165:335-8.
16. Rikitake Y, Kawashima S, Takeshita S, Yamashita T, Azumi H, Yasuhara M, Nishi H, Inoue N, Yokoyama 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.
17. Weber C, Erl W, Weber PC. Lovastatin induces differentiation of Mono Mac 6 cells. Cell Biochem Funct 1995; 13:273-7.
18. Vaughan CJ, Gotto AM, Basson CT. The evolving role of statins in the management of atherosclerosis. J Am Coll Cardiol 2000; 35:1-10.
19. Laufs U, Fata VL, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG-CoA reductase inhibitors. Circulation 1998; 97:1129-35.
20. Corsini A, Pazzucconi F, Arnaboldi L, Pfister P, Fumagalli R, Paoletti R, Sirtori CR. Direct effects of statins on the vascular wall. J Cardiovasc Pharmacol 1998; 31:773-8.
21. Soma MR, Donetti E, Parolini C et al. HMG CoA reductase inhibitors. In vivo effects on carotid intimal thickening in normocholesterolemic rabbits. Arterioscler Thromb 1993; 13:571-8.
22. Yasunari K, Maeda K, Minami M, Yoshikawa J. HMG-CoA reductase inhibitors prevent migration of human coronary smooth muscle cells through suppression of increase in oxidative stress. Arterioscler Thromb Vasc Biol 2001; 2:937-42.
23. Cuthbert JA, Lipsky PE. Sterol metabolism and lymphocyte responsiveness: inhibition of endogenous sterol synthesis prevents mitogen-induced human T cell proliferation. J Immunol 1981; 126:2093-9.
24. Cutts JL, Bankhurst AD. Suppression of lymphoid cell function in vitro by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by lovastatin. Int J Immunopharmacol 1989; 11:863-9.

25. Kurakata S, Kada M, Shimada Y, Komai T, Nomoto K. Effects of different inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, pravastatin sodium and simvastatin, on sterol synthesis and immunological functions in human lymphocytes in vitro. Immunopharmacol 1996; 34: 51-61.
26. Rosenfeld ME, Ross R. Macrophage and smooth muscle cell proliferation in atherosclerotic lesions of WHHL and comparably hypercholesterolemic fat-fed rabbits Arteriosclerosis 1990; 10: 680-7. .
27. Becker S, Warren MK, Haskill S. Colony-stimulating factor-induced onocyte survival and differentiation into macrophages in serum-free cultures. J Immunol 1987; 139: 3703-9.
28. Metcalf D. The molecular control of cell division, differentiation commitment and maturation in haemopoietic cells. Nature 1989; 339:27-30.
29. Sakai M, Miyazaki A, Hakamata H, Sato Y, Matsumura T, Kobori S, Shichiri M, Horiuchi S. Lysophosphatidylcholine potentiates the mitogenic activity of modified LDL for human monocyte-derived macrophages. Arterioscler Thromb Vasc Biol 1996; 16: 600-5.
30. Aviram M, Hussein O, Rosenblat M, Schlezinger S, Hayek T, Keidar S. Interactions of platelets, macrophages, and lipoproteins in hypercholesterolemia: antiatherogenic effects of HMG-CoA reductase inhibitor therapy. J Cardiovasc Pharmacol 1998; 31: 39-45.
31. Wagner AH, Kohler T, Ruckschloss U, Just I, Hecker M. Improvement of nitric oxide-dependent vasodilatation by HMG-CoA reductase inhibitors through attenuation of endothelial superoxide anion formation. Arterioscler Thromb Vasc Biol 2000; 20: 61- 9.
32. Chen L, Haught WH, Yang B. Preservation of endogenous antioxidant activity and inhibition of lipid peroxidation as common mechanisms of antiatherosclerotic effects of vitamin E, lovastatin and amlodipine. J Am Coll Cardiol 1997; 30: 569-75.
33. Pietsch A, Erl W, Lorenz RL. Lovastatin reduces the expression of the combined adhesion and scavenger receptor CD36 in human monocytic cells. Biochem. Pharmacol 1996; 52: 433.
34. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995; 92:657-71.
35. Bellosta S, Via D, Canavesi M, Pfister P, Fumagalli R, Paoletti R. HMG-CoA reductase inhibitors reduce MMP-9 secretion by macrophages. Arterioscler Thromb Vasc Biol 1998; 18:1671-8.
36. Ballantyne CM, Herd JA, Dunn JK, Jones PH, Farmer JA, Gotto AMJ. Effects of lipid lowering therapy on progression of coronary and carotid artery disease. Curr Opin Lipidol 1997; 8: 354- 61.
37. Nofer JR, Tepel M, Kehrel B. Low-density lipoproteins inhibit the Na+/H+ antiport in human platelets: a novel mechanism enhancing platelet activity in hypercolesterolemia. Circulation 1997; 95:1370-7.
38. Essig M, Nguyen G, Prie D, Escoubet B, Sraer JD, Friedlander G. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors increase fibrinolytic activity in rat aortic endothelial cells. Circ Res 1998; 83:683-90.
39. Colli S, Eligini S, Lalli M, Camera M, Paoletti R, Tremoli E, Vastatins inhibit tissue factor in cultured human macrophages: a novel mechanism of protection against atherosclerosis. Arterioscler Thromb Vasc Biol 1997; 17:265-72.
40. Mitchell LB, Powell JL, Gillis AM, Kehl V, Hallstrom AP. AVID Investigators.Are lipid lowering drugs also Antiarrythmic drugs? An analysis of the antiarrythmics versus implantable defibrillators (AVID) trial. J M Coll Cardiol 2003; 42:81-7.
41. Siu CW, Lau CP, Tse HF. Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. Am J Cardiol 2003; 92:1343-5.
42. Maron DJ, Fazio S, Linton MF. Current Perspectives on statins. Circulation 2000; 101:207-13.
43. Lamers JM, Hartog JM, Verdoew PD, Hulsmann WC. Dietary fatty acids and myocardial function. Basic Cardiol 1987; 82(Suppl 1):209-21.
44. Pound EM, Kang JX, Leaf A. Partiotioning of polyunsaturated fatty acids, which prevent cardiac arrythmias into phospholipid cell membranes. J Lipid Res 2001; 42:346-51.
45. Tsiara S, Elisaf M, Mikhialipids DP. Early Vascular benefits of statins therapy. Curr Med Res Opin 2003; 19:540-56.
46. Mohler ER, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking disease in patients with peripheral arterial disease. Circulation 2003; 108:1481-6.
47. Kuroskwa EM. Nitric oxide therapies in vascular disease. Curr Pharm Des 2002; 8:55-156.
48. Stamler JS, Loh E, Roddy MA, Currie KE, Creager MA. Nitric oxide regulates basal systemic and pulmonary vascular resistance in healthy humans. Circulation 1994; 89:2035-40.
49. Huhle G, Abletshauser C, Mayer N, Weidienger G Harenberg G, Heene DL. Reduction of Platlet activity markers in type 2 hypercholesterolimic patients by a HMG- CoA reductase inhibitor. Thromb Res 1999; 95:29-234.
50. Hernandez-PO, Perez SD. Navarro–Antazolin J, Sanchez-Pascuala R,Hernandez G, Diaz C, et.al Effects of the 3- hydroxy 3- methylglutyralCoA reductase inhibitors Atorvastatin and Simvastatin on the expression of the endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. J Clin invest 1998; 101:2711-9.
51. Visser M, Pahor M, Taffe DR, Goodpaster BH, Simonsick EM, Newman AB, et al. Relationship of interleucins-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the health ABC study. J Gerontol A Biol Sci med sci 2002; 57: M326-32.
52. Node K, Fujita M, Kitikaze M, Hori M, Liao JK. Shjort term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiopathy. Circulation 2003:108:839-43.
53. Stuve O, Youseff S, Steinmann L, Zamwill SS. Statins as potential therapeutic agents in neuroinflammatory disorders. Curr Opin Neurol 2003; 16:393-401.
54. Young XUY, Chan KA, Liao JK, Ravid S, Blatt CM. Long term statin use and psychological well-being. J Am Coll Cardiol 2003; 42:690-7.
55. Jakobisiak M, Golab J. Potiental antitumour effects of statins. Int J Oncol 2003; 23:1055-69.
56. Cauley JA, Zmauda JM, Lui LY, Hillier TA, Ness RB, Stone KL, Cummings SR, Bauer DC . Lipid lowering drug use and breast cancer in older women: a prospective study. J Womens Health (Larchmt) 2003; 12:749-56.
57. Collison EA, Kleer C, Wu M, DE A, Gambhir SS, Merajver SD, Kolodney MS. Atorvastatin prevents RhoC isoprenalytion, invasion and metastasis in human melanoma cells. Mol Cancer Ther 2003; 2:941-8.
58. Wang PS, Solomon DH, Mogun H, Avorn. J. HMG CoA reductase inhibitors and the risk of hip fractures in elderly patients .JAMA 2000; 283:3211-6.
59. Bauer DC, Mundy GR, Jamal SA, Black DM, Cauley JA, Ensrud KE, van der Klift M, Pols HA. Use of statins and fracture: results of 4 prospective studies and cumulative meta observational studies and controlled trials. Arch Intern Med 2004; 164:146-52.
60. McGwin GJr, Owsley C, Curcio CA, Crain RJ. The association between statin use and age related Maculopathy. Br J Opthalmol 2003; 87:1121-5.
61. Shishehbor MH, Brennam ML, Aviles RJ, Fu X, Penn MS, Sprecher DL, et al. Statins promote potent systemic antioxidant effects through specific inflammatory pathways. Circulation 2003; 108:426-31.
62. McDermott MM, Guralnik JM, Greenland P, Pearce WH, Criqui MH, Liu K, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003; 107:757-61.
63. Pelat M, Dessy C, Massion P, Desager JP, Feron O, Balligand JL. Rosuvastatin decreases caveolin-1 and improves nitric oxide

dependent heart rate and blood pressure variability in apolipoprotein E-/- mice in vivo. Circulation 2003; 107:2480-6.

64. Jones SP, Gibson MF, Rimmer III DM, Gibson TM, Sharp BR, Lefer DJ. Direct vascular and cardioprotective effects of rosuvastatin a new HMG-CoA reductase inhibitor. JAm Coll Cardiol 2002; 40:1172-8.
65. Efthimiodis AP, Psirropoulos D, Efthimidis T, Lefkos-N. Action of statins upon thrombogenesis, fibrinolysis and inflammation in coronary patients. Hippokratia 2002; 6:186-92.
66. Tanaka K, Yasohara M, Suzumura K, Narita H, Suzuki T. Effects of fluvastatin and its major metabolities on low-density lipoprotein oxidation and cholesterol esterification in macrophages. Jpn J Pharmacol 2001; 86:289-96.
67. Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. Circulation 2001; 103:1191-3.
68. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C- reactive protein levels: The pravastatin inflammation/CRP evaluation (PRINCE). A randomized trial and cohort study. JAMA 2001; 286:64-70.
69. Serruys PW, De Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, et al. Fluvastatin for revention of cardiac events following successful first percutaneous coronary intervention: A randomized controlled trial. JAMA 2002; 287:3215-22.
70. Romano M, Mezzetti A, Marulli C, Ciabattoni G, Febo F, Di Ienno S, et al. Fluvastatin reduces soluble P-selectin and ICAM-1 levels in hypercholesterolemic patients: Role of nitric oxide. J Investig Med 2000; 48:183-9.
71. Katoh M, Kurosawa Y, Tanaka K, Watanabe A, Doi H, Narita H. Fluvastatin inhibits O2-and ICAM-1 levels in a rat model with aortic remodeling induced by pressure overload. Am J Physiol Heart Circ Physiol 2001; 281:655-60.
72. Niwa S, Totsuka T, Hayashi S. Inhibitory effect of fluvastatin, an HMG-CoA reductase inhibitor, on the expression of adhesion molecules on human monocyte cell line. Int J Immunopharmacol 1996; 18:669-75.
73. Kreuzer J, Bader J, Jahn L, Hautmann M, Kubler W, Von Hodenberg E. Chemotaxis of the monocyte cell line U937: dependence on cholesterol and early mevalonate pathway products. Atherosclerosis 1991; 90:203-9.
74. Romano M, Diomede L, Sironi M, Massimiliano L, Sottocorno M, Polentarutti N, et al. Inhibition of monocyte chemotactic protein-1 synthesis by statins. Lab Invest 2000; 80: 1095-100.
75. Shiomi M, Ito T. Effect of cerivastatin sodium, a new inhibitor of HMG-CoA reductase, on plasma lipid levels, progression of atherosclerosis, and the lesional composition in the plaques of WHHL rabbits. Br J Pharmacol 1999; 126:961-8.
76. Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, et al. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrixproteinases and tissue factor in vivo and in vitro. Circulation 2001; 103:276-83.
77. Fukumoto Y, Libby P, Rabkin E, Hill CC, Enomoto M, Hirouchi Y, et al. Statins alter smooth muscle cell accumulation and collagen content in established atheroma of watanabe heritable hyperlipidemic rabbits. Circulation 2001; 103: 993-9.
78. Nishimura T, Vaszar LT, Faul JL, Zhao G, Berry CJ, Shi L, et al. Simvastatin rescues rats from fatal pulmonary hypertension by inducing apoptosis of neointimal smooth muscle cells. Circulation 2003; 108:1640-5.
79. Guijarro C, Blanco-Colio LM, Ortego M, Alonso C, Ortiz A, Plaza JJ, et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase and isoprenylation inhibitors induce apoptosis of vascular smooth muscle cells in culture. Circ Res 1998; 83: 490-500.
80. Inoue I, Goto S, Mizotani K, Awata T, Mastunaga T, Kawai S, et al. Lipophilic HMG-CoA reductase inhibitor has an anti-inflammatory effect: reduction of MRNA levels for interleukin-1beta, interleukin-6, cyclooxygenase-2, and p22phox by regulation of peroxisome proliferator-activated receptor alpha (PPAR alpha) in primary endothelial cells. Life Sci 2000; 67:863-76.
81. Cutts JL, Bankhurst AD. Suppression of lymphoid cell function in vitro by inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A reductase by lovastatin. Int J Immunopharmacol 1989; 11:863-9.
82. Kurakata S, Kada M, Shimada Y, Komai T, Nomoto K. Effects of different inhibitors of 3-hydrox-3-methylglutary1 coenzyme-A (HMG-CoA) reductase, pravastatin sodium and simvastatin, on sterol synthesis and immunological functions in human lymphocytes in vitro. Immunopharmacology 1996; 34:51-61.
83. Steimle V, Siegrist CA, Mottet A, Lisowska-Grospierre B, Mach B. Regulation of MHC class II expression by interferon-gamma mediated by the transactivator gene CIITA. Science 1994; 265:106-9.
84. Rosenson RS, Tangney CC, Casey LC. Inhibition of proinflammatory cytokine production by pravastatin. Lancet 1999; 353:983-4.
85. Grip O, Janciauskiene S, Lindgren S. Pravastatin down-regulates inflammatory mediators in human moncytes in vitro. Eur J Pharmacol 2000; 410:83-92.
86. Musial J, Undas A, Gajewski P, Jankowski M, Sydor W, Szczeklik A. Antiinflammatory effects of simvastatin in subjects with hypercholesterolemia. Int J Cardiol 2001; 77:247-53.
87. Wassmann S. Laufs U, Muller K, Konkol C, Ahlbory K, Baumer AT, et al. Cellular antioxidant effects of atorvastatin in vitro and in vivo. Arterioscler Thromb Vasc Biol 2002; 22:300-5.
88. Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998; 47:1129-35.
89. Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995; 333:621-7.
90. Kureishi Y, Luo Z, Shiojima I, bialik A, Fulton D, Lefer DJ, et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med 2000;6:1004-10. Erratum in: Nat Med 2001; 7:129.
91. Scalia R, Gooszen ME, Jones SP, Hoffmeyer M, Rimmer DM, Trocha SD, et al. Simvastatin exerts both anti-inflammatory and cardioprotective effects in Apo E deficient mice. Circulation 2001; 103: 2598-603.
92. Giroux LM, Davignon J, Naruszewicz M. Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocyte-derived macrophages. Biochem Biophys Acta 1993; 1165:335-8.
93. Wilson SH, Simari RD, Best PJ, Peterson TE, Lerman LO, Aviram M, et al. Simvastatin preserves coronary endothelial function in hypercholesterolemia in the absence of lipid lowering. Arterioscler Thromb Vasc Biol 2001; 21:122-8.
94. Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, et al. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. Circulation 2001; 103:276-83.
95. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J. Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflamma- tion, metalloproteinases, and cell death in human carotid plaques: Implications for plaque stabilization. Circulation 2001; 103:926-33.
96. Bustos, C, Hernandez-Presa usa MA, Ortego M, Tunon J, Ortega L, Perez F, et al. HMG-CoA reductase inhibition by atorvastatin reduces neointimal inflammation in a rabbit model of atherosclerosis. J Am Coll Cardiol 1998; 32:2057-64.
97. Rosenson RS. Non-lipid lowering effects of statins on atherosclerosis. CurrCardiol Rep 1999; 1:225-32.
98. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: Implications for cardiovascular event reduction. JAMA 1998; 279:1643-50.
99. Park JK, Muller DN, Mervaala EM, Dechend R, Fiebeler A, Schmidt F, et al. Cerivastatin prevents angiotensin-II-induced renal injury independent of blood pressure and cholesterol-lowering effects. Kidney Int 2000; 58:1420-30.

100. Hernandez-Perera O, Ferez-Sala D, Navarvo-Antolin J, Sanchez Pascuala R, Hernandez G, Diaz C, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. J Clin Invest 1998; 101:2711-9.

101. Puccetti L, Bruni F, Bova G, Cercignani M, Pompella G, Auteri A, et al. Role of platelets in tissue factor expression by monocytes in normal and hypercholesterolemic subjects. In vitro effect of cerivastatin. Int J Clin Lab Res 2000; 30:147–56.

102. Buemi M, Allegra A, Corica F, Aloisi C, Giacobbe M, Pettinato G, et al. Effect of fluvastatin on proteinuria in patients with immunoglobulin A nephropathy. Clin Pharmacol Ther 2000; 67:427-31.

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