PLEIOTROPIC EFFECTS OF STATINS AND CARDIOVASCULAR BENEFITS

Floriana Elvira Ionică [1], *Maria Moţa* [2], *Diana Protasiewicz* [3], *Eliza Gofiţă* [1]

[1] Faculty of Pharmacy, University of Medicine and Pharmacy Craiova
[2] Faculty of Medicine, University of Medicine and Pharmacy Craiova
[3] Clinical Emergency Hospital Craiova

Abstract

Pleiotropic effects of a drug are other actions than those for which the drug was specially designed. These effects may be related or unrelated to the primary mechanism of action of the drug, and they are usually unanticipated.

Pleiotropic effects may be undesirable (such as side effects or toxicity), or beneficial, as is especially the case with statins. Pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques. These and several other emergent properties could act in concert with the potent low-density lipoprotein cholesterol-lowering effects of statins to exert early as well as lasting cardiovascular protective effects. Understanding the pleiotropic effects of statins is important to optimize their use in treatment and prevention of cardiovascular disease.

Key words*: statin, endothelial dysfunction, atherosclerotic plaques*

Introduction

First clinical experience with administration of statins was held in 1976, and since the 80 trials were initiated extensive research of the effects of statins in U.S. clinics. The occurrence of inhibitors 3-hydroxy-3-metilglutaril-coenzyme A reductase inhibitors (statins) has revolutionized treatment hipercolesterolemiei. In the liver, statins specifically inhibit competitive, reversible HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA (hydroxymethylglutaryl-coenzyme A) to mevalonic acid, limiting step in cholesterol synthesis. The decrease in cholesterol synthesis, statins also reduce, the formation of lipoproteins, especially LDL and VLDL. By inhibiting the conversion of HMG-CoA to L-mevalonic acid, statins prevent the synthesis of important isoprenoids, such as farnesyl-pyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), which are precursors of cholesterol biosynthesis[1, 26] (Figure 1).

In addition, inhibition of cholesterol causes a compensatory increase in LDL receptor expression in the liver, which binds circulating LDL particles and VLDL remnants, removing them from circulation. These effects result in less total cholesterol, LDL-cholesterol and serum triglycerides.

In addition to marked lipid-lowering, beneficial effect of statins occurs through other mechanisms, called pleiotropic (non-lipidic): anti-inflammatory, antiproliferative,

immuno-suppressive effects, positive influence on rheological parameters and the thrombogenesis, improve endothelial function [1] (Table 1).

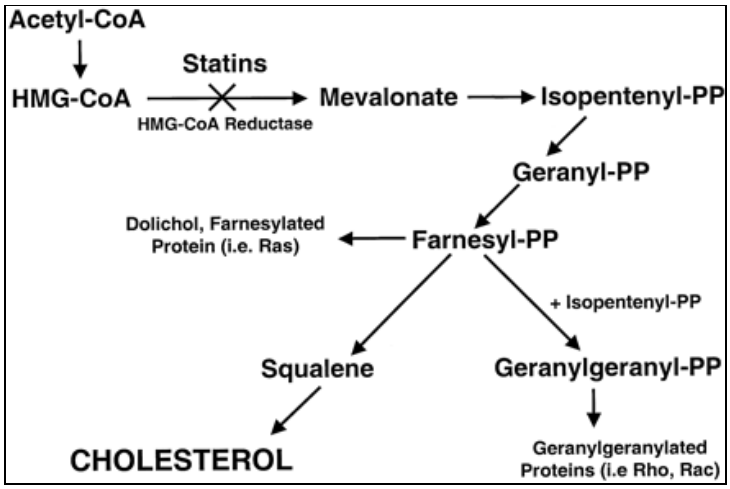

Figure 1. Cholesterol biosynthetic pathway. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins decreases the synthesis of isoprenoids and cholesterol. PP indicates pyrophosphate [Modification by reference 26].

Table 1. Pleiotropic effects of statins
(M.Alegret and J.S. Silvestre. Timely Top Med Dis 2007)

Effect	Benefit
Increased synthesis of nitric oxide synthesis	Improvement of endothelial dysfunction
Inhibiting the release of free radicals decrease of endothelin-1	
Inhibition of oxidation of LDL cholesterol	
Up-regulation of endothelial progenitor cell	
Reduction in the number and activity of inflammatory cells	Reduction of the inflammatory response
C-reactive protein levels reduction	
Reduction of cholesterol accumulation in macrophages	Stabilization of ateroma plaque
Inhibition of production metalloproteinase	
Reducing adhesion/ aggregation platelet	Reduction thrombogenic response
Reducing fibrinogen concentration	
Reduction of blood viscosity reduction	
Increased synthesis of nitric oxide synthesis	

Antiinflammatory effect

Lately is more evidence about the role of inflammation and immune reactions of the organism in the genesis of atherosclerosis and its complications. In an article published in 1999 by R. Ross atherosclerosis is presented as a complex inflammatory process characterized by the presence of monocytes, macrophages and T-lymphocytes in atherosclerotic plaques. Inflammatory cytokines secreted by macrophages and lymphocytes-T may influence endothelial function, smooth muscle cell proliferation, collagen degradation, and thrombosis [2]. Large clinical trials have shown that statins

possess anti-inflammatory effect shown in aseptic inflammation in the infectious nature.

The mechanisms that influence inflammatory effect:

- reduce the number of inflammatory cells in atherosclerotic plaques,
- inhibits intercellular adhesion molecules ICAM-1,
- reduce P-selectin expression in endothelial cells,
- inhibit the expression of monocytes chemotactic protein-1 (MCP-1) and interaction with cytokines, particularly interleukin-1 and interleukin-6.

Antiinflammatory effect of statins is independent of their action on cellular cholesterol biosynthesis. Markers of inflammation, particularly C-reactive protein (CRP), interleukin-6, tumor necrosis factor-α (TNF-α) and ICAM-1, were associated with increased risk for primary and recurrent cardiovascular events and were proposed as risk factors for cardiovascular disease [3].

The incidence of complications of atherosclerosis and death is in direct relationship with serum levels of C-reactive protein. It is increased in patients with coronary ischemia and is a predictor of future cardiovascular events in healthy persons. Statins reduce CRP levels at patients with hypercholesterolemia [26]. The data CARE study which showed that administration of Pravastatin during the 5 years has contributed significantly reduce CRP levels [4]. Study AFCAPS / TexCAPS demonstrated to reduce CRP levels in patients treated with statins group, which had major acute coronary events. The data PRINCE (Pravastatin Inflamation/ CRP Evaluation Trial) confirmed significant reduction in CRP levels by ~ 13% during treatment with statins in both primary prevention and in the secondary. The results CARE, AFCAPS / TexCAPS, treatment with statins do not only reduce CRP levels, but also has clinical benefits in healthy persons with high levels of CRP. On purpose to evaluate the usefulness of administration of statins in primary prevention trial was initiated JUPITER (Justification for the risk of statins in Primary prevention, an Intervention Trial Evaluating Rosuvastatin) [5]. The results of this study will provide information on the usefulness of administration of statins in primary prevention in people with high levels of CRP, but not hypercholesterolemia. The anti-inflammatory effect of statins clearly improve the development of coronary, brain and peripheral vessels atherosclerosis. This effect was best demonstrated in patients with angina pectoris and acute myocardial infarction treated with statins (MIRACL trial).

Antithrombotic effect

Acute formation of thrombus in atherosclerotic plaques rupture site is the most common cause of acute coronary events. Thrombogenic potential of atherosclerotic plaques is determined by the interaction of platelets, coagulation factors, local coronary flow parameters and vascular wall structure.

Antithrombotic effect is achieved through several mechanisms: reduction of platelet aggregation, reduction of thrombin synthesis, activation of fibrinolysis and decreasing the level of tissue plasminogen activator inhibitor (PAI 1) with increased synthesis of tissue plasminogen activator (t-PA) activity in endothelial cells and reduce tissue factor (TF). Hypercholesterolemia is associated with a state of hypercoagulation and increased

platelet reactivity, caused in particular by increasing LDL-C. Several studies have shown to reduce platelet reactivity and the levels of thromboxane A2 (TXA2) and increased synthesis of prostacyclin (TXA2 antagonist) in treatment with statins.

Statins inhibit expression and activity of tissue factor in cultured monocytes / macrophages and endothelial cell cultures. The study ATROCAP (Atorvastatin and ThROmbogenity of the carotid Atherosclerotic Plaque Study, 2002) administration of atorvastatin at a dose 20 mg / day for 4-6 months led to significant reduction of TF levels and activity atherosclerotic plaques after endarterectomy. As a result of inhibition of TF action after treatment with statins reduce thrombin synthesis and this effect is independent of lipid-lowering effect [6].

Studies in vitro have noted that statins positively influence the fibrinolytic system, reducing levels of PAI-1 and increasing levels of tissue plasminogen activator in cultured smooth muscle cells and endothelial cells [7]. Numerous in vivo studies have investigated the effect of treatment with statins on the fibrinolytic system. The results were different, in some studies statins reduced plasma levels of PAI-1 [8]. Increased levels of fibrinogen and plasma viscosity increased risk of cardiovascular events in patients with or without ischemic heart disease. Currently there are conflicting data on the effects of statins on fibrinogen and plasma viscosity.

Improving endothelial function

One of the most important pleiotropic effects of statins are their ability to influence endothelial dysfunction. Endothelial dysfunction occurs at early stages of atherosclerosis, and in advanced stages involved in the progression of atherosclerotic plaque and them rupture. Statins improve endothelial dysfunction in two ways: by normalizing lipid spectrum and by direct action on the endothelium. The last is considered pleiotropic effect. For the first time in 1994 found that administration of Pravastatin in doses 10 to 20 mg/day for 6 months improved endothelium-dependent dilation of coronary arteries in patients with hypercholesterolemia. In another study administration of Lovastatin in doses 20 mg/day in patients with atherosclerosis obviously improved endothelium-dependent dilation of coronary arteries after 6 months of treatment. The ability of statins to restore endothelial function is observed so the treatment of short duration and low-dose treatment. Administration of atorvastatin at a dose of 10 mg/day in postmenopausal women with hypercholesterolemia over 8 weeks led to the increase in FMD (flow mediated Dilatation) brachial artery after only 2 weeks of treatment, which subsequently rose to 4th week and 8th. The study RECIFE (Reduction of cholesterol in Ischemia and Function of the Endothelium trial) treatment with Pravastatin in 40 mg/day dose during the 6 weeks resulted in increased FMD in patients with acute coronary syndrome. Change FMD did not correlate with reduced total cholesterol and LDL-C, suggesting the idea that improving endothelial function is not related to lipid-lowering effect of statins. A higher dose of simvastatin inhibits Rho-associated coiled-coil containing protein kinase (ROCK) activity and improves endothelial function to a greater extent than the combination of a lower dose of simvastatin and ezetimibe despite comparable

lipid-lowering efficacy. The effect of simvastatin on ROCK activity was statistically significant even after controlling for changes in LDL-C, supporting the concept that inhibition of ROCK may contribute to some of the lipid-independent or pleiotropic effects of statin therapy. It remains to be determined, however, whether these lipid-independent effects of statins contribute to the outcome benefits of statin therapy [26].

Mechanisms to improve endothelial dysfunction under the influence of treatment with statins:

- increased synthesis of nitric oxide in the endothelium after activation of NO synthase [9]
- vasodilatation occurs as a result of the normalization of endothelial properties; has been established that the degree of improvement in capacity vasodilation of arteries of muscular type correlates with the lowering of LDL-C. More pronounced vasodilator effect was observed at lowering serum LDL-C of less than 100mg/dl.
- return of endothelial barrier function, which prevent the intrusion of foreign elements (bacteria, fat) per se and in macrophages.
- statins inhibit the production of superoxide and hydroxyl radicals, due to their antioxidant effect, leading to improved endothelium-dependent vasodilatation.

Statins restore normal synthesis of nitric oxide through various mechanisms:

- regulating the activity of endothelial NO synthase (eNOS),
- inhibits degradation eNOS by reducing the formation superoxide,
- posttranslatory activation of eNOS by phosphorylation,
- reducing caveolin-1 which is a specific inhibitor of eNOS [9].

Endothelial dysfunction is present in patients with diabetes and insulin resistance and is characterized by reduced vascular NO effective action.

Statins modulate the release and action of vasoconstriction substances endothelin and angiotensin-II. They have direct action on the production of endothelin-1, by reducing the precursor pre-endothelin-1, leading to decrease vascular resistance and improving coronary blood flow and systemic. Statins stimulates production of vasodilator substance -prostacyclin and reduce the aterogen potential of lipoproteins. Hydroxylated metabolites of atorvastatin inhibit oxidation of LDL, VLDL and HDL. Atorvastatin suppresses oxidized LDL capture by monocytes, which play an important role in the development of atherosclerosis.

Statins have **anti-ischemic action on the myocardium**. This effect is directly related to the restoration of normal endothelial function. Anti-ischemic effect is characteristic of all statins and is manifested by reducing the frequency of accesses of angina pectoris and signs of myocardial ischemia at physical effort [11].

Stabilization of atherosclerotic plaque

Local inflammation contributes to weakening the fibrous capsule and instability of atherosclerotic plaque. Rupture of vulnerable plaque leads to the formation of occlusion thrombus and is the major cause of acute coronary syndromes. It is known that more than 75% of acute coronary syndrome cases occur due to crack unstable atheroma

and coronary artery thrombosis [12]. Easier break atherosclerotic plaques that narrow the vascular lumen up to 50%.

Describes three components of the atherosclerotic process stability:

- atheromatous core size and composition,
- thick fibrous capsule covering the core,
- the presence of inflammation reactions.

Triggers of atherosclerotic plaque rupture are physical effort, stress, high blood pressure. In the unstable atherosclerotic plaque region is a chronic inflammation process, with a high activity of macrophages and T-cell accumulation in fibrous capsule rupture region, followed by release of substances of inflammation: cytokines, tumor necrosis factor-α, interleuchina-1-β and interferon-γ (gamma). These substances directly induce cell apoptosis or raise awareness among cells in apoptosis. Monocytes and macrophages causes apoptosis by direct cell-cell contact. These inflammatory stimulus induce apoptosis in smooth muscle cells of vessels and endothelial cells of the intima.

Secretion and activation of matrix metalloproteinase causes degradation of fibrous capsule and plaque prone to rupture.

Stabilization of atherosclerotic plaque after treatment with statin takes place and due lipid-lowering effect. Experimental studies have shown that lowering cholesterol with diet reduces the number of macrophages, inhibits expression of matrix metalloproteinases (MMP) and increased interstitial collagen content in the atherosclerotic lesions. Cholesterol reduction in patients treated with statins was associated with increased density of fibrous tissue, increased interstitial collagen content, reduced MMP activity in atherosclerotic plaque. Lowering levels of LDL-C levels by statins may help stabilize atherosclerotic plaque by reducing the size of lipid core or modifying its physicochemical properties.

Stabilization of atherosclerotic plaque takes place and because non-lipid effects of statins. Mechanisms of stabilizing atherosclerotic plaque in the treatment with statins:

- lipid core volume reduction and change their structure,
- strengthening fibrous capsule by increasing collagen content,
- reducing inflammation through reducing the number and the activity of macrophage,
- decreased neovascularisation and artherial intima calcification,
- lower thrombogenic potential of the plaque,
- improve endothelial function,
- inhibiting the formation and removal of calcium deposits in atherosclerotic plaque.

Following the studies was hypothesized that lipid-lowering treatment with statins might reduce the fat content of the core plaque, thereby reducing its risk for rupture. Stabilization of atherosclerotic plate reduces the incidence of acute coronary syndromes.

Stroke prevention

Approximately 80-85% of cases are ischemic attacks caused by atherosclerosis, but more often the main artery atherothrombosis or penetrating cerebral arteries (lacunar ictus) and thromboembolic of cardiac origin (with thrombotic masses in the cavities of the heart or valves), or artheryal (brahiocephalic basin and aortic arch), where embolism may be a

fragment of atherosclerotic plaque. The presence of common risk factors (hypertension, age, smoking, diabetes, obesity) underlying the importance of atherosclerosis in the pathogenesis of stroke. In the CARDS study (Collaborative Atorvastatin Diabetes Study) reduced LDL-C levels were associated with a low risk of 48% of stroke in patients with diabetes [11]. According to this study, LDL-C may be used as a marker for assessing the effectiveness of statin therapy in reducing stroke. Reducing non-fatal incidence of stroke is based on non-lipid effects of statins [1]. Lowering blood cholesterol through diet or drugs (except statins) has not reduced the incidence of brain events and the administration of Clofibrat increased their risk. In the group of patients treated with statins is observed to reduce the risk of developing stroke, especially non-fatal in up to 50% [13].

Possible mechanisms for reducing the risk of stroke after treatment with statins are: inhibiting the process of inflammation in atherosclerotic plaque and vessel wall, the stabilization atherosclerotic plaque, antithrombotic and antioxidant effects, improved endothelial function and vascular reactivity. Greater focus is given to improve reactivity of cerebral arteries under the influence of statins, as a result of increase in nitric oxide secretion by vascular endothelium. Since pleiotropic effects of statins above have a universal character, it is necessary that the **neuroprotective effect** of statins. NO regulates cerebral perfusion by relaxing vascular smooth muscle relaxation and statins improve peripheral vessels after 2 weeks of treatment. NO produced by cerebral microvascular network helps reduce the risk of dementia in patients who are in therapy with statins [14]. NOS I and nNOS take active part in the oxidative damages the brain parenchyma in cases of cerebral ischemia or reperfusion, and NOS II produced by astrocytes, neutrophils and microglia with pro-inflammatory mediators and cytokines (TNF-α, IL1β, IL-B6) participate actively on stimulate inflammatory process [15].

Statins decrease the activity of Rho-kinase, which regulates the formation of fibers, smooth muscle contraction and cell migration playing an important role in the following pathological conditions: inflammation and vascular remodeling, hypertension, vasospasm, atherosclerosis. Suppression of Rho-kinase in vivo and in vitro resulted in increased expression eNOS and increase cerebral blood flow. According to recent clinical data statins improve clinical course after subarachnoidal hemorrhage [16].

Epidemiological studies suggest that some statins, especially Pravastatin and Lovastatin, have **a beneficial effect on the development of Alzheimer's disease**.

After 6 months of treatment with acetylcholinesterase inhibitors and with or without Atorvastatin 80 mg/day significant benefits on depressive symptoms and cognitive function were obtained in patients treated with atorvastatin group. Recent have been initiated 2 studies: CLASP (Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease) with simvastatin administration during the 18 months and LEAD (Lipitor's Effect in Alzheimer's Disease) with donepezil and with or without Atorvastatin for 18 months, which have to determine the role of statins in reducing or stopping the progression of Alzheimer's

disease [17]. To prove the role of statins in secondary prevention of stroke and the influence of active lipid-lowering treatment on cerebrovascular complications in patients with stroke or recurrent stroke in history, but without ischemic heart disease, were initiated 2 large clinical trials: PROSPER (Pravastatin 40 mg/day) and SPARCL (Atorvastatin 80 mg/day).

According to existing studies, statins have other effects: **immunosuppressive effect** [18], supporting vasculogenesis and reduces the recurrence of cardiovascular events [19], **stimulates osteoblast differentiation** and reduced risk of fracture [20], reduced cardiac hypertrophy [21], **antitumor effects** by inhibiting tumor cell growth and mitigation of invasive and metastatic properties of cancer cells [22], **reduce the severity sepsis** and improve survival of these patients [23], **effect nephroprotective** [24,25].

Conclusions

Although the possibility that statins may have effects pleiotrope was initially received with great skepticism, the knowledge gained over the last few years has moved the focus of these effects. Many of the pleiotropic effects of statins act independently of LDL cholesterol reduction, correlate poorly or not at all with changes in LDL-cholesterol, occur rapidly and are reversible upon discontinuation of therapy. Direct effects in the absence of changes in total cholesterol or LDL cholesterol have been shown both in vitro and in vivo. Pleiotropic effects of statins are still investigating to determine fully their role in preventing cardiovascular events. Results of several clinical trials in progress, aimed specifically pleiotropic effects of statins should highlight their clinical relevance and importance.

REFERENCES

1. Calabro P., Yeh E.T. The pleiotropic effects of statins. Curr Opin Cardiol, vol.20, p.541-546, 2005.

2. Ross R: Atherosclerosis: an inflammatory disease. *N Engl J Med* 340: 115-126, 1999.

3. Stancu C, Sima A: Statins: mechanism of action and effects. J Cell Mol Med, vol.5, no. 4, p. 378-387, 2001.

4. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, Flaker GC, Braunwald E, for the Cholesterol and Recurrent Events (CARE) Investigators: Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation* 98: 839-844, 1998.

5. Ridker PM, on behalf of the JUPITER Study Group: Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 109: 2292-2297, 2003.

6. Cortellaro M., Cofrancesco E., Arbustini E. et al. Atorvastatin and thrombogenity of the carotid atherosclerotic plaque: The ATROCAP study. Thromb Haemost, vol.88, p.41-47, 2002.

7. Bourcier T., Libby P.: HMG CoA reductase inhibitors reduce plasminogen activator inhibitor-1 expression by human vascular smooth muscle and endothelial cells. Arterioscler Thromb Vasc Biol, vol.20, p.556-562, 2000.

8. Dangas G., Smith D.A., Unger A.H. et al. Pravastatin: an antithrombotic effect independent of the cholesterol-lowering effect. Thromb Haemost, vol.83, p. 688-692, 2000.

9. Feron O., Dessy C., Desager J.P. et al. Hydroxy-methylglutaryl-coenzyme A reductase inhibition promotes endothelial nitric oxide synthase activation through a decrease in caveolin abundance. Circulation, vol.103, no1, p.113-118, 2001.

10. Takemoto M., Liao J.K. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors.ArteriosclerThtombVasc Biol, vol.21, p.1712-1719, 2001.

11. Colhoun H, Betteridge D, Durrington P. et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet, vol. 364, no. 9435, p. 685-696, 2001.

12. Shah P.K. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol, vol.41, p.15-22, 2003.

13. Thomas J. Wang, Philimon Gona, Martin G. Larson et al. Multiple Biomarkers for the Prediction of First Major Cardiovascular Events and Death. The NEW ENGLAND JOURNAL of MEDICINE, vol.355, p.2631-2639, 2006.

14. Jick H., Zornberg G.L., Jick S.S. et al. Statins and risk of dementia. Lancet, vol. 356(9242), p.1627-1631, 2000.

15. Forster C., Clark H.B., Ross N.E. Inducible nitric oxide synthase expression in human cerebral infarcts. Acta Neuropathol (Berl), vol. 97, no.3, p. 215-220, 1999.

16. Rikitake Y., Kim H-H., Huang Z. et al. Inhibition of Rho Kinase (ROCK) leads to increased cerebral blood flow and stroke protection. Stroke, vol.36, p.2251-2257, 2005.

17. Kivipelto M., Solomon A., Winblad B. Statin therapy in Alzheimer's disease. Lancet Neurol, vol.4, p, 521-522, 2005

18. Hakamada-Taguchi R., Uehara Y., Kuribayashi K et al. Inhibition of hydroxymethylglutaryl-coenzyme a reductase Th1 development and promotes Th2 development. Circ Res, vol. 93, p.948-956, 2003.

19. Walter D.H., Rittig K., Bahlmann F.H. et al. Statin therapy accelerates reendothelialization: a novel effect involving mobilization and incorporation of bone marrow-derived endothelial progenitor cells. Circulation, vol.105, p.3017-3024, 2003.

20. Maeda T., Matsunuma A., Kurahashi I. et al. Induction of osteoblast differentiation indices by statins in MC3T3-E1 cells. J Cell Biochem, vol.92, p.458-471, 2004.

21. Maack C., Kartes T., Kilter H. et al. Oxygen free radical release in human failing myocardium is associated with increased activity of rac1-GTPase and represents a target for statin treatment. Circulation, vol.108, p.1567-1574, 2003.

22. CHAN K.K., OZA A.M., SIU L.L. The statins as anticancer agents. Clin Cancer Res, 2003, vol.9, p.10-19.

23. ALMOG Y., SHEFER A., NOVACK V. et al. Prior statin therapy is associated with a decreased rate of severe sepsis. Circulation, 2004, vol.110, p.880-885.

24. Agarwal R., Curley T.M. The role of statins in chronic kidney disease. Am J Med Sci, vol.330, p.69-81, 2005.

25. Vieira J.M., Rodrigues L.T., Mantovani E. et al. Statin monotherapy attenuates renal injury in a salt-sensitive hypertension model of renal disease. Nephron Physiol, vol.101, p.82-91, 2005.

26. Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. Trends Mol Med. 2008;14:37–44.

27. Ping-Yen Liu, Yen-Wen Liu, Li-Jen Lin, Jyh-Hong Chen and James K. Liao. Evidence for Statin Pleiotropy in Humans: Differential Effects of Statins and Ezetimibe on Rho-Associated Coiled-Coil Containing Protein Kinase Activity, Endothelial Function, and Inflammation. Circulation 2009;119;131-138.