Pleiotropic Effects of Statins

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In the last decades, substantial progress has been made in understanding the relationship between lipid disorders and the prevention of cardiac ischemic disease. The identification of new therapeutic targets and new lipid-modifying agents expands treatment options. Statins have been described as the principal and most effective class of drugs to reduce serum cholesterol levels and cardiovascular events in patients with or without coronary artery disease. 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. It was found during recent years that many of statins, positive effects could not be explained simply by lowering of atherogenic lipids. There were shown also to exist non-lipid-modifiable effects of statins called pleiotropic ones, which could be responsible for this additional benefit. The most important positive pleiotropic effects of statins are antiinflammatory, antiproliferative, and antithrombotic ones, improving endothelial dysfunction and others.

Key Words: Statins ● Pleiotropic effects ● Atherosclerosis

INTRODUCTION

Cardiovascular disease, which includes coronary heart disease, stroke, and peripheral arterial disease, is the leading cause of death worldwide. In 2001, cardiovascular diseases contributed to nearly one third of all global deaths. According to World Health Organization statistics, more than 16 million people die of cardiovascular disease each year, and 7.2 million deaths in 2001 were caused by heart disease. By the year 2020, approximately 25 million deaths annually worldwide are expected from cardiovascular disease, and almost half of those deaths (11.1 million) will be from coronary heart disease.

Statins were discovered in 1976 when Endo et al. found that a product of mould Penicillium citricum was able to inhibit activity of one of the enzymes in the cascade of cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase). This substance was used for further name statins (va-}

CHARACTERISTICS OF STATINS

Statins are a chemically and pharmacologically di-
verse group of drugs that share the ability to inhibit hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase), the enzyme that controls the rate-limiting step of cholesterol synthesis, but this inhibition is followed by other subsequences associated with the mevalonate pathway (Figure 1).

The clinically beneficial effects of statins were usually assumed to result from their ability to reduce cholesterol synthesis. In 1994, the landmark Scandinavian Simvastatin Survival Study (4S) established the benefits of a HMG-CoA reductase inhibitor on mortality in patients with atherosclerosis. In accord with traditional acceptance of atherosclerosis as a consequence of lipid disorders, post-hoc analysis of the 4S trial suggested that the benefit provided by simvastatin in individual patients indeed related to the magnitude of change in low-density lipoprotein cholesterol. Subsequent studies, however, differed with this conclusion even as they affirmed the clinical benefits of statins as a class on cardiovascular morbidity and mortality in patients with or without established atherosclerotic disease. These studies raised questions about additional beneficial effects of statins, because mevalonate, the product of the enzyme reaction, is the precursor not only of cholesterol but also of many nonsteroidal isoprenoid compounds, and inhibition of HMG-CoA reductase may produce pleiotropic effects (see Figure 1).

Indeed, the mevalonate pathway yields a series of isoprenoids that are vital for diverse cellular functions. These isoprenoids include: isopentenyl adenosine, present in some types of transfer RNA; dolichols, required for glycoprotein synthesis; and polyisoprenoid side chains of ubiquinone and heme A, involved in electron transport. Several proteins have also been identified that are post-translationally modified by the covalent attachment of mevalonate-derived isoprenoid groups-either farnesyl or geranylgeranyl pyrophosphate. These proteins must be prenylated as a prerequisite for membrane association, which is required for their function. Members of this family are involved in a number of cellular processes, including cell signaling, cell differentiation and proliferation, myelination, cytoskeleton dynamics,
and endocytotic/exocytotic transport.

Hence, through the inhibition of HMG-CoA reductase, statins may affect a variety of processes; this may help to explain their non-lipid-related pharmacologic properties. Indeed, several recent in vitro and in vivo experiments have demonstrated that HMG-CoA reductase inhibitors have antiatherosclerotic effects that are not related to lipid lowering. Because of their broad effects and their extremely low incidence of side effects, statins might even be seen as the new aspirin.12

The currently available statins are lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and rosvastatin. Cerivastatin was withdrawn from the market in 2001 due to increased number of fatal rhabdomyolyses.13

It seems that the process of metabolization of statins is important from the safety point of view. Several of them are metabolized via cytochrome P450 (see Table 1).14-16 However, only a small proportion of rosuvastatin and fluvastatin are metabolized via cytochrome P450 2C9, so there is no high risk of dangerous drug interactions associated with the use of these statins as well. Patients taking several drugs metabolized by the same cytochrome P450 are at higher risk of side effects of statins. Only two of the currently available statins are hydrophilic – pravastatin and rosuvastatin – this could also be important in prevention of “increased fluidity” of muscle cell membrane and then increased risk of myopathy or even rhabdomyolysis.16 Antioxidant activities of statins differ (the greatest is observed in atorvastatin, with surprisingly much lower activity observed in rosvastatin) and might be cardioprotective in two different ways. Firstly, statins decrease oxidation of LDL cholesterol particles, and secondly, they have protective effect on myocyte membrane in ubiquinone deficiency which may appear during long-term statin therapy.16,18

The main action of statins is to specifically and reversibly inhibit HMG-CoA reductase, which controls the rate-limiting step in cholesterol synthesis. Several studies have compared lipid-lowering effects of different statins head to head. In one of the latest, STELLAR study, rosuvastatin in the dosage of 40 mg was more effective than all currently available statins in all recommended doses. LDL cholesterol was lowered by 55% with rosuvastatin 40 mg daily.19

These differences in efficacy were confirmed in a meta-analysis of 164 studies published in 2003. Here also, the different statins showed a two- to three-fold difference in the extent of LDL cholesterol lowering across the dosage range.20

The effect on HDL cholesterol was compared as well in the STELLAR study. It was shown that rosuvastatin had the greatest potency to increase HDL cholesterol, followed by simvastatin and atorvastatin (maximal increase 9.6% vs 6.8% vs 5.7%).21 The recent study of Bevilacqua showed different results.22 Compared were fluvastatin extended release form 80 mg daily, which was superior to atorvastatin 20 mg daily. However, in general, statins have much lower potency to increase HDL in comparison with fibrates or nicotinic acid. Surprisingly, it was shown in the MIRACL trial that high-density lipoprotein, but not low-density lipoprotein cholesterol levels, influenced short-term prognosis after acute coronary syndrome, and this finding suggested that the clinical benefit of atorvastatin after acute coronary syndrome was mediated by qualitative changes in the

| Table 1. Characteristics of statins |
| Dose range (mg/dL) | Atorvastatin | Lovastatin | Pravastatin | Simvastatin | Fluvastatin | Rosuvastatin |
| 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 (small proportion) | Cytochrome p-450 2C9 (small proportion) |
| Hydro/lipophilic properties | lipophilic | lipophilic | hydrophilic | lipophilic | lipophilic | hydrophilic |
LDL particle and/or by non-lipid (pleiotropic) effects of the drug.23

PLEIOTROPIC EFFECTS – DEFINITION

Drugs usually have multiple effects; through an analogy with single genes which affect more than one system or determine more than one phenotype, they are currently referred to as "pleiotropic effects" (from the Greek “pleion,” meaning more, and “tropos,” meaning direction or turn). These may be related or unrelated to primary mode of action of the drug. Pleiotropic effects may emerge during preclinical and clinical studies in drug development, but more often than not, they are discovered a posteriori long after the therapeutic agent is marketed (the same situation occurs in use of statins). They may be undesirable and recognized as adverse side effects, they may be neutral, or they may be beneficial, enhancing the desirable effect of a drug.24

ANTIATHEROGENIC PLEIOTROPIC EFFECTS OF STATINS

The most important pleiotropic antiatherogenic effects of statins are improvement of endothelial dysfunction, antioxidative properties, antiinflammatory, antiproliferative and antithrombotic effects and neangiogenesis.25 Statins inhibit by blocking HMG-CoA reductase, and also by blocking synthesis of geranylated proteins responsible for proliferation and migration of smooth muscle cells from vessel media to intima and their conversion from contractile to reparatory type which are causes growth of atherosclerotic plaque. Also, synthesis of farnesylated proteins is inhibited, that is why also activity of nuclear factor kappa B is decreased. This factor plays very important role in the initiation of inflammatory process-atherosclerosis is inflammatory disease.26

Statins and Endothelial Dysfunction

Abnormal endothelium-dependent vasomotor responses predict the long-term progression of atherosclerosis and associated coronary events, as well as events after vascular surgery.27,28 Statins are able to increase nitric oxide synthesis and improve blood flow dependent upon endothelium, as was shown in study of Marchesi et al. with atorvastatin and other statins.29,30

Statins and Antiinflammatory Effects

Recent research has shown that inflammation plays a key role in coronary artery disease and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, and activation of inflammation can elicit acute coronary syndromes. Elevated markers for inflammation such as CRP, interleukin-6, intercellular adhesion molecule-1 (ICAM-1), and serum amyloid A have been associated with increased risk for the first and recurrent cardiovascular events.31 Many experimental and clinical studies confirmed significant reduction of CRP measured by high sensitive method (hs CRP). The higher the baseline value of CRP, the higher the decrease that has been observed, e.g. in the PROVE IT study.32 In that study, decrease of hs CRP achieved 89% in the atorvastatin group and 85% in the pravastatin group. Generally, the greatest decreases of hs CRP were observed after treatment with atorvastatin or rosuvastatin. Increased levels of CRP were associated with more pronounced monocyte migration and increased LDL uptake by macrophages.33

Statins and Plaque Growth

Statins have antiproliferative effects and inhibit transformation of contractile smooth muscle cells to reparatory-type cells and their migration from arterial media into intima.34 Statins decrease synthesis of extracellular matrix and proteins Rac1, Rho A as well, and by this means decrease plaque growth.35

Substantial differences have been found between the statins. For example, in the ASAP study, it was shown that at the highest therapeutic dose, two years of treatment with atorvastatin reduced the thickness of the arterial wall, while after simvastatin treatment, the thickness of the arterial wall continued to increase.36 Similar results were achieved in the ARBITER study when atorvastatin and pravastatin were compared.37 In a very recent study, REVERSAL, where intravascular ultrasound method was used to quantify atherosclerosis, after 18 months of therapy with atorvastatin 80 mg daily, volume of the atherosclerotic plaque slightly decreased, while the volume of the plaque continued to increase during therapy with pravastatin 40 mg daily.38
Statins and Angiogenesis
Statins are able to activate proteinkinase Akt in endothelial cells and thereby stimulate activity of endothelial nitric oxide synthethase leading to increased NO production and neoangiogenesis. Stimulation of proteinkinase Akt improves myocardial aerobic metabolism. Statins increase also the level of angiopoetine. 39

Statins and Plaque Rupture
Statins significantly reduce metalloproteinases activity, mainly of MMP1 and MMP3, which play important roles in plaque rupture or fissuration. 40 Decrease of blood pressure observed during long-term treatment with statins lead to improvement of rheology and arterial stiffness. 41

Statins and Thrombosis
Statins have capacity to decrease global fibrinolytic activity of the blood, decrease activity of PAI-1 and inhibit thrombine generation. Data regarding influence of statins on fibrinogen levels are not so convincing. 42

Statins and Plaque Stability
There were several pleiotropic effects of statins described which should be responsible for the stability of the atherosclerotic plaque. Nevertheless, the most important finding for plaque stability is the combination of lipid-lowering effects with pleiotropic ones (especially decrease of plaque lipid core size and inhibition of inflammatory reaction). 43

Possible Negative Pleiotropic Effects of Statins
Inhibition of HMG-CoA reductase leads not only to decreased synthesis of cholesterol but also affects synthesis of other substances. Besides these positive pleiotropic effects, there is probably also a negative one, namely, inhibition of geranyl pyrophosphate synthesis and subsequently dekaprenyl-4-bensoate, which is a precursor of coenzyme Q10. Coenzyme Q10 (ubiquinone, ubidekarenone) is a very important substance in myocardial energetic metabolism and the stability of cell membrane as well; when deficient, myocytes could be prone to damage in the form of myopathy or myositis, or even rhabdomyolysis. 44 Deficiency of coenzyme Q10 will appear usually after longer duration of treatment and may also be dependent on type of statin and its dosage. Given the fact that statins will be prescribed more widely (“... statins to every patient with documented coronary artery disease...” Yusuf S, Lancet 2002), it is very important to consider the safety of such therapy. 45 Statin therapy is long-term (even life-long, following evidence-based medicine), so the risk of adverse effects might be increased. More clinical studies are needed in order to confirm the beneficial effects of coenzyme Q10 substitution in long-term statin therapy. The International College of Cardiology, in its scientific statement, recommended use of statins preferably in conjunction with coenzyme Q10 in order to prevent possible myopathy. 46

The recently published hypothesis by Moosmann and Behl has identified a possible role of deficiency of selenium and association with possible adverse effects of statins, namely myopathy and polyneuropathy. 47 They noted that the pattern of side effects associated with statins resembled the pathology of selenium deficiency, and postulated that the mechanism lay in a well-established but often overlooked biochemical pathway – the isopentylation of selenocysteine-tRNA. A negative effect of statins on selenoprotein synthesis does seem to explain many of the enigmatic effects and side effects of statins, in particular, statin-induced myopathy.

In a recent study, Silver et al. evaluated left ventricular diastolic function with Doppler echocardiography before and after statin therapy. Statin therapy worsened diastolic parameters in most patients; coenzyme Q10 supplementation in patients with worsened diastolic function with statin therapy improved parameters of diastolic function. 48

Similar results were confirmed in the study of Kumar et al. in more than 100 studied subjects (the study of Silver et al. evaluated only 14 patients). 49

What is very important to say is that statins are generally very well tolerated drugs and a remarkably safe class of lipid lowering agents. These data probably lead to the fact that in the United Kingdom simvastatin is now available in pharmacies without medical prescription. 50

PLEIOTROPIC EFFECTS OF STATINS IN NON-ATHEROSCLEROTIC DISEASE

Antiproliferative and antiinflammatory effects of
statins have raised questions about possible use of statins in diseases other than atherosclerosis, cardiovascular and non-cardiovascular. Many clinical studies are in progress which probably should enlighten us on their relative clinical relevance and importance. Some of the diseases involved in this research are listed in Table 2. 

**CONCLUSIONS**

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.

Although the possibility that statins might have pleiotropic effects was met at first with healthy scepticism, the vast amount of knowledge accrued over the past few years has moved these effects into the spotlight. Pleiotropic effects of statins are numerous and varied, they may add to the desirable effect of a drug or be undesirable and interfere with the treatment. 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 so-called 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 e.g. osteoporosis, rheumatoid arthritis, connective tissue diseases, etc.) that could yield benefits in terms of targeting and developing novel strategies that will address the residual burden of atherosclerotic complications that plague even those individuals who achieved current lipid goals.

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高血脂治療藥物 STATIN 的多重作用

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近十年來，對於改善血脂肪異常與預防缺血性心臟病之間的研究逐漸開展。對於建立新的治療標的與研發新的高血脂治療藥物也拓展臨床治療的選擇。不論病人是否具有冠狀動脈心臟病，STATIN 已成為降低血膽固醇值與心血管疾病併發症最主要及最有效的藥物。最近研究指出，STATIN 在治療心血管疾病的好處，不僅僅只從降低血膽固醇值方面解

釋。一些改善血脂肪異常以外的效果，如抗發炎、抗增生及抗血栓效果，以及改善內皮細胞功能等，也扮演部份角色，本文將對這些改善血脂肪異常外之多重作用 (extra-lipid pleiotropic effects) 作概略介紹。

關鍵詞：高血脂治療藥物、降血脂外多重作用、冠狀動脈心臟病。