Bratisl Lek Listy 2009; 110 (10)
664 – 668

REVIEW

Statins: The Drugs for the 21st Century?

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Abstract: This review summarizes the current evidence on beneficial effect of statins on the atherogenesis and the preventive potential of coenzyme Q 10 to avoid statin-induced myopathy.
Statins, originally discovered in molds are the most effective medication to decrease the low-density cholesterol (LDL-C) which is the key participant in atherogenesis. Statins accomplish this by inhibiting the hydroxymethyl glutaryl coenzyme A reductase, an enzyme that is rate limiting for cholesterol biosynthesis. Inhibition of HMG CoA reductase stimulates in the liver the LDL receptors. The result is is an increased clearance of LDL particles from the bloodstream and by this mechanism statins have proved to be highly effective in reducing the cardiovascular risk, as amply documented in clinical studies confirming inhibition of atherosclerosis. Additional beneficial effect of statins occurs by modulation of endothelial functions and by diminishing vessel wall inflammation. Statins reduce the level of the C-reactive protein, a strong predictor of adverse cardiovascular events. Beneficial effects of statins on endothelial dysfunction and synthesis of nitric oxide NO were described. Different statin preparation might differ in their antioxidant effects *(Fig. 2, Ref. 46)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: heart disease, statins, side effects, myopathy, coenzyme Q10, low density lipoproteins.

Japanese investigators hypothesized that some microorganisms may produce inhibitors of hydroxymethyl glutaryl coenzyme A reductase (HMG CoA) as a defense against other microbial agents. Mevalonate is a precursor of many substances required by microorganisms for integrity of their cell wall (cytoskeleton). When they searched thousands of species of microorganisms, the biochemists isolated mevastatin, a molecule produced by Penicillium citrinum. Unexpectedly, this molecule inhibited not only mevalonate but also the synthesis of cholesterol (Fig. 1).

This discovery initiated an enormous interest in the United States that had been under the spell of excessive cardiovascular (CV) mortality. The first commercially available statin, lovastatin was introduced by Merck pharmacological industry. Statins were confirmed to effectively reduce the low-density cholesterol (LDL-C). The Japanese biochemist Akira Endo was awarded thirty years later the prestigious Lasker Prize for the discovery of an agent that blocks the synthesis of cholesterol.

Pharmacological industry continuosly modifies statin molecules (1). After lovastatin, fluvastatin, pravastatin and simvastatin it has been atorvastatin, cerivastatin, pitavastatin and, recently the allegedly most effective rosuvastatin. Imaging studies (intravascular ultrasound) reported regression of atheromatous plaques in secondary clinical trials with Rosuvastatin (2). Statins belong now to the world's second most commonly prescribed medicine (after cancer drugs). They were used by 24 mllion North Americans in 2003–2004.

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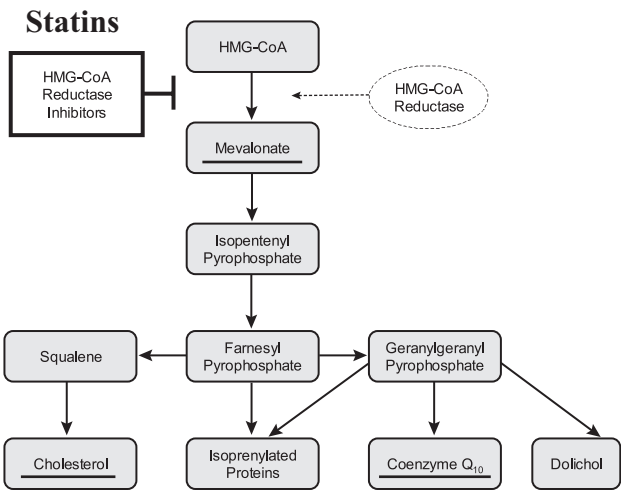

Fig. 1. Metabolic interventions of statins. Statins by inhibition of HMG-CoA reductase lower the formation of mevalonate, cholesterol and coenzyme Q10.

While statins are the most effective agent in the management of atherogenesis, they are only one in a series of other medications that act by different mechanisms: Fibrates, bile acid binding resins and the most recent addition of ezetimibe, an inhibitor of intestinal absorption of cholesterol.

Statins and lipoprotein metabolism

Statins lower cholesterol by inhibiting HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Inhibition of this

enzyme in the liver stimulates LDL receptors, resulting in an increased clearance of LDL from the bloodstream. Statin therapy continues to increase among US adults and this has led to substantial improvements in LDL-C control (1). LDL-C quality rather than quantity exerts an important effect on CV risk. LDL comprise multiple sub classes with discrete size, density and physicochemical behavior that influence their atherogenicity. Small dense LDLs are predictors of CV mortality. Different effectiveness of various statins on atherogenesis may be related to their specific effect on LDL subclasses (3). In 2006 there were published seven trials of statins in nearly 43,000 patients (4). In patients without clinical diagnosis of coronary heart disease (CHD) statin therapy decreased future major coronary and cerebrovascular events but not the overall mortality. Another meta analysis in 2007 pooled six statin trials including 110,271 patient-years (5). Compared with moderate statin therapy, intensive statin administration reduced all-cause mortality in patients with recent acute coronary events but not in patients with stable CHD. Use of statins was significantly associated with a decreased risk of incidence or recurrence of atrial fibrillation in patients with a history of prevous atrial fibrillation or after an acute coronary syndrome (6). Statin therapy provided effective protection for non-hemorrhagic stroke (7).

In 2008 the reports related to the effect of statins in CHD included about ten meta analyses and hundred thousands of clinical cases (7–15). These clinical studies confirmed statins to lower LDL-C and to reduce major adverse CV events in patients with systemic hypertension, in type two diabetes, in patients undergoing cardiac intervention and in chronic kidney disease.

Anti-inflammatory and antioxidant effects of statins

Recent clinical studies are suggesting that statins may affect the CV system beyond their influence on the LDL. Statins also act on the immune functions and on vascular inflammation. Many of the beneficial pleiotropic effects of statins are the result of modulated endothelial function and inhibition of inflammatory processes.

The established model of atherogenesis envisioned a normal CV system as smooth blood vessels with unobstructed blood flow. When LDL-C particles reached a critical limit they accumulated with the platelets on the endothelial surface, generating a plaque with cholesterol. This obstruction reduced oxygen delivery to target organs. When the heart muscle or brain became compromised, the result was a myocardial infarction or a stroke.

We now know that this popular model is incomplete. The vessel wall contains cells that actively communicate with their environment. These cells are under the influence of immune mechanisms and exposed to the adverse effect of oxygen free radicals. When the immediate environment is unfavorable it contributes to the deposition of oxidized LDL deposits in atheromatous plaques.

There are at least three components involved in atherogenesis: 1) A high level of circulating LDL particles, 2) Altered immunological mechanisms contributing to vessel wall inflammation, and, 3) Dysbalance in oxygenation/ reduction resulting in an oxidative stress and oxidation of LDL particles (16–17) (Fig. 2).

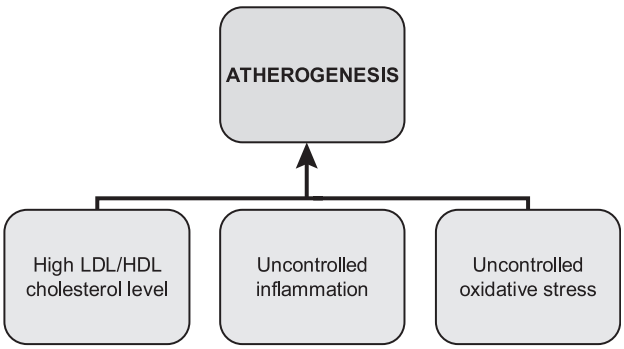

Fig. 2. Three decisive factors in atherogenesis: high LDL/HDL cholesterol concentration in blood plasma, uncontrolled inflammation of artery intima and uncontrolled activity of free radicals (oxidative stress).

All three atherogenic components synergistically contribute to CHD. Thus, in addition to LDL-C it is also the C-reactive protein (CRP) that is a strong predictor of CV events. CRP is one of the acute phase reactants. Its level rises dramatically during processes of inflammation.

Ridker (18) grouped patient populations according to total cholesterol/ HDL-C levels and CRP in blood into progressively rising quintiles. CV risk at the lowest CRP and highest total/ /HDL-C was four times higher compared to individuals who have normal both values. Conversely, when the total/HDL-C is at the lowest level and CRP is highly elevated, the CV risk increases two times. Remarkably, patients with the highest both total/HDL-C and CRP have nine times higher CV risk compared to people with normal values.

In another impressive clinical study Ridker (19) documented the protective effect of statins in a selected group of 18,000 individuals who had normal LDL-C but elevated CRP. In this JUPITER trial of apparently healthy individuals without hyperlipidemia but with elevated CRP, rosuvastatin significantly reduced the incidence of future major CV events.

The production of endothelium-derived nitric oxid (NO) synthesized by nitric oxid synthase (NOS) plays a central role in the maintenance of endothelium homeostasis. NO is an important messenger molecule involved in many physiological and pathological processes. Reactive oxygen species directly inactivate NOS (20). Limitation of vascular reactive oxygen species can restore endothelial function in humans. After a series of animal studies it was demonstrated that after pravastatin treatment the NOS activity was significantly potentiated in humans also (21). Different statin preparation might differ in their antioxidant effects and effects on NO production.

It is interesting that the protective effect of statins appears to be independent of the level of HDL-C. Research in molecular biology of these processes (22–25) suggests that by inhibiting the HMG-CoA reductase statins also reduce the synthesis of isoprenoids. These are important lipid attachments for intracellular signaling molecules. Statins may exert cholesterol-indepen-

dent or pleiotropic effect by inhibiting these small guanosine triphosphate (GTP) binding proteins that are involved in cell proliferation.

Side effects of statins

In the United States the prevalence of obesity is continuously rising but CVD mortality is declining. This opposite trend suggests that medications like statins are having an important impact. Along with the positive reports and the tendency to presribe statins to ever larger groups of population, it is essential to consider potential side effects of interference with cholesterol metabolism.

Using statins as potential first-line pharmacological agents to reduce cholesterol has ben the subject of some controversy. Cholesterol is a lipid present in the cell membranes and subcellular organelles. It plays a key role in maintaining membrane fluidity, thereby influencing transmembrane signals. Cholesterol in the brain accounts for about 25 % of total body stores. It promotes myelin formation and synaptogenesis. Also, it serves as a building block for all steroid hormones. The primary site of action of statins is the liver but some statins inhibit cholesterol synthesis also in other tissues, including the brain.

Recently, statin uncontrolled use in childhood has been subject to an intensive discussion. Because of growing evidence that atherosclerosis begins at an early age and that obesity and hypercholesterolemia in children may increase the risk of life-time CVD, the American Academy of Pediatrics in July 2008 recommended statins among potential first line agents for childhood hypercholesterolemia, This induced a strong controversy (26). Concern was expressed that a child's brain at the age of eight years remains in development and that long-term pharmacotherapy in childhood may adversely affect immune functions, hormonal balance and the overall energy metabolism.

Regarding potential side efects of statins, in meta analyses the data of over 70,000 patients were analyzed (27). Serious events were infrequent. Statin therapy was associated with greater odds of adverse effects compared with placebo but with substantial clinical benefit. Treating one thousand patients with statins would prevent 37 clinical CV events but only five adverse effects would be observed.

Regarding cancerogenesis, authoritative trials documented at best only a neutral effect on cancer. In meta analyses including 6,662 cancers and 2,407 cancer deaths, statins did not increase or reduce the incidence of cancer (28). This has been confirmed in most recent meta analyses (29–31) that reported no effect of statins on cancer risk. It is of interest that adding ezetimibe to statin (combination therapy) for aortic stenosis resulted in excess of incidental cancers (32). This dictates a need for caution: Ezetimibe interferes with intestinal absorption not only of cholesterol but also of other molecules that could effect the growth of cancer cells.

Two of the most troubling statin side effects include muscle pain (myalgia), muscle disease (myopathy) and liver abnormalities, most prominently expressed in an elevation of the serum aminotransferase.

Statins block production of farnesyl pyrophosphate, an intermediate in the synthesis of coenzyme Q_{10} (Fig. 1). This, along with the role of Co Q_{10} in mitochondrial energy production has prompted the hypothesis that statin-induced Co Q_{10} deficiency is instrumental in the pathogenesis of statin-induced myopathy (33–36).

Co Q_{10} is an oil-soluble antioxidant. It forms a very effective redox system composed of ubiquinol (reduced form), semiquinone radical and ubiquinone (oxidized form).

Co Q_{10} is a component of the electron transport chain in mitochondria and it participates in aerobic cellular respiration, generating energy in the form of ATP.

Its synthesis in the human body decreases with age. Meta-analysis of several clinical studies has shown that statin treatment reduces circulating levels of Co Q_{10} (34). In some reports the decrease of plasma Co Q_{10} level was very high, about 50 %. This could be related to statins lowering the plasma LDL. Co Q_{10} is mainly transported by LDL but a decrease is also found in platelets and in lymphocytes of statin treated patients. This indicates a possible inhibition of Co Q_{10} synthesis (37–40), in addition to its effect on transport functions.

In patients with chronic heart failure (not necessarily induced by CHD) a drop in Co Q_{10}, along with a decrease in total cholesterol was an independent predictor of mortallity (41).

There are also some indications, considered contradictory that statin treatment affects muscle Co Q_{10} levels. Statin-induced myopathy could then by attributed to a deficient supply of energy in the form of ATP to the muscle. Subsequently it is being postulated that Co Q_{10} supplementation would reduce the degree of muscle pain associated with statin treatment. Initial attempts in administering Co Q_{10} to statin-treated patients with myopathic symptoms had a positive outcome: pain severity significantly decreased after 30 days of statin therapy (42, 43). Co Q_{10} is not only an essential co-factor in the mitochondrial electron transport pathway, but also a strong lipid-soluble antioxidant which has a well acknowledged antioxidant role by counteracting LDL and nitric oxide oxidation in the cardiovascular system (44, 45).

Recently there were three randomized trials with Co Q_{10} supplemenation in hypercholesterolemic patients treated with statins (46). The results of these trials have been contradictory: one seemed to support supplementation with Co Q_{10} but the other two studies did not. Present evidence does not support Co Q_{10} supplementation in statin-induced myopathy. Nevertheless, there are no known risks to Co Q_{10} supplementation at pharmacological dosage.

Conclusion

Discovery of pharmacological value of statins was a complex trail that led from an agent produced by molds to protect themselves from other microorganisms, to a very effective medication. Statins reduce the LDL-C and they help to prevent CV disorders. Remarkably, statins while being of microbial origin, counter adverse effects of inflammation. There are internists and cardiologists who are convinced that many millions of apparently healthy people, even with normal cholesterol may benefit

from statins. This suggests a controversial dilemma: Is it time to place cholesterol-lowering statins in every medicine cabinet? Many other clinicians are more careful, pointing to the beneficial metabolic role cholesterol has in the animal organism. They warn of potential side effects of drastic universal cholesterol lowering in subjects with no evidence of heart disease. Sarcastically, they claim that "protective effect of statins does not warrant these should be used to fortify drinking water or to become another active ingredient added to commercially marketed cereals."

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Received January 4, 2009.
Accepted June 26, 2009.