ATORVASTATIN: EFFICACY IN ATHEROSCLEROSIS AND CARDIOVASCULAR DISEASE WITH EMPHASIS TO ATHEROGENESIS

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ATORVASTATIN: EFIKASNOST U ATEROSKLEROZI I KARDIOVASKULARNOJ BOLESTI SA OSVRTOM NA ATEROGENEZU

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SAŽETAK

Atorvastatin je sintetski, selektivni inhibitor HMG-CoA reduktaze. Ovaj statin blokira pretvaranje HMG-CoA u mevalonat. Posledica te blokade je redukcija količine LDL-C, ukupnog holesterola, Apo B i triglicerida u serumu. Od nelipidnih dejstava atorvastatina najvažnije je antiinflamatorno koje je praćeno smanjenjem količine proinflamatornih citokina, hemiokina i faktora rasta.

Klinička ispitivanja pokazuju da atorvastatin (10 mg/d) izaziva veće smanjenje koncentracije LDL-C od simvastatina (10mg/d), fluvastatina (20 mg/d) i lovastatina (20 mg/d) u plazmi. Istovremeno, najkraće vreme za ciljne vrednosti LDL-C u serumu postižu se sa atorvastatinom i sa dozama manjim od simvastatina, fluvastatina i lovastatina. Rosusvastatin, za razliku od atorvastatina, izaziva veću redukciju količine LDL-C u serumu. Atorvastatin redukuje, takodje, i sistemski inflamatorni marker CRP u serumu.

U bolesnika sa akutnim koronarnim sindromom agresivna (80 mg/d) terapija atorvastatinom redukuje ponovne ishemijske dogadjaje uglavnom ponovne simptomatske ishemije koje zahtevaju rehospitalizaciju kao i moždani udar. Atorvastatin, u dužem vremenskom periodu (1–3 godine) čak i u najmanjim dozama od 10 mg/d smanjuje ukupne kardiovaskularne dogadjaje, ukupne koronarne dogadjaje i moždani udar. U bolesnika sa koronarnom bolešću agresivna terapija atorvastatinom (80 mg/d) redukuje progresiju koronarne ateroskleroze i posle akutnog koronarnog sindroma bolja je prevencija od smrtnog ishoda i najznačajnijih kardiovaskularnih dogadjaja u odnosu na standardnu terapiju pravastatinom (40 mg/d). Agresivna terapija, takodje, atorvastatinom (80 mg/d) skraćuje debljinu intima-media u karotidama, ali ne i standardna terapija simvastatinom (40 mg/d) u bolesnika sa familijarnom hiperholesterolemijom. U pojedinačnoj dozi atorvastatin se može dati u bilo koje doba dana sa ili bez hrane. Atorvastatin se dobro podnosi i ima prihvatljiva neželjena dejstva čak i u najvećim dozama od 80 mg/d.

Zaključak: Atorvastatin je jedan od najefikasnijih hipolipemijskih lekova koji danas postoji. Efikasnost atorvastatina je posledica i njegovog antiinflamatornog dejstva. Atorvastatin je efikasan u prevenciji kardiovaskualrnih bolesti (infarkt miokarda, revaskularizacione procedure i angina) i hiperlipoproteinemijama. Prema tome, ne treba da se čudimo što se danas najčešće koristi kao hipolipoproteinemijski lek.

Ključne reči: atorvastatin, hipolipoproteinemijsko dejstvo, antiinflamatorno dejstvo, prevencija kardiovaskularne bolesti, terapija hipolipiproteinemija

Skraćenice: Apo-B- apolipoprotein-B, COX-2- ciklooksigenaza -2, CRP- C reaktivni protein, HMG-CoA - 3-hidroksi-3-metilglutaril koenzim A, HDL-C - lipoproteini visoke gustine, IDL-C - lipoproteini intermdeijarne gustine, IL-1 - interleukin-1, IL-6 - interleukin-6, IL-8 - interleukin-8, M-CSF – makrofagnih kolonija stimulatni faktor, LDL-C - lipoproteini niske gustine, TG- trigliceridi, TNF-alfa - tumor nekrozis faktor-alfa, VLDL-C - lipoproteini vrlo niske gustine

ABSTRACT

Atorvastatin is synthetic, selective inhibitor of HMG-CoA reductase. The statin blocks the conversion of HMG-CoA to mevalonate. The consequence of this blockade is the reduction of serum LDL-C, total cholesterol, Apo B and triglycerides levels. The most important of non-lipid effects of atorvastatin is its antiinflamatory action accompanied with reduced levels of proinflammatory cytokines, chemokines and growth factors.

Clinical trials show that atorvastatin (10 mg/d) produces greater decrease in plasma LDL-C levels than simvastatin (10 mg/d), fluvastatin (20 mg/d) and lovastatin (20 mg/d). At the same time, atorvastatin therapy resulted in a greater percentage of patients defined LDL-C target goals at an earlier median timepoint with lower doses than simvastatin, fluvastatin and lovastatin. Rosuvastatin compared with atorvastatin causes greater reduction of serum LDL-C levels. Atorvastatin reduces also the serum systemic inflammatory marker CRP.

In patients with acute coronary syndrome the aggressive (80 mg/d) therapy with atorvastatin reduces the recurrent ischemic events mostly recurrent symptomatic ischemia requiring rehospitalization and stroke. In longer follow-up time (1–3 years) atorvasastatin even in the smallest doses of 10 mg/d lowers total cardiovascular events, total coronary events and stroke. For patients with coronary heart disease the aggressive therapy with atorvastatin (80 mg/d) reduces the progression of coronary atherosclerosis and after acute coronary syndrome provides greater protection against death and major cardiovascular events than standard regime with pravastatin (40 mg/d). Aggressive therapy also with atorvastatin (80 mg/d) is associated with regression of carotid intima-media thickness, but not with regime of simvastatin (standard therapy with doses of 40 mg/d) in patients with familiar hypercholesterolemia. As a single dose it can be administered at any time of ten day with or without the food. Atorvastatin even in the highest doses of 80 mg/d is well tolerated and has an acceptable safety profile.

Conclusion- Atorvastatin is one of the most powerful hypolipidemic drugs currently available. The beneficial effects of the statin are associated with antiinflamatory action as well. Atorvastatin therapy is very effective in prevention of the cardiovascular disease (myocardial infarction, revascularization procedures and angina) and hyperlipoproteinemia. Therefore, it is not surprising that atorvastatin became the most widely prescribed lipid lowering drug.

Key words: atorvastatin, lipid lowering effect, antiinflammatory effect, prevention of cardiovascular disease, therapy of hyperlipidemia.

Abbreviations: Apo B- apolipoprotein B, COX-2 – cyclooxygenase-2, CRP – C-reactive protein, HMG-CoA – 3-hydroxy-3-methylglutaryl coenzyme A, HDL-C – high density lipoprotein, IDL-C – intermediate density lipoprotein, IL-1 – interleukin-1, IL-6 – interleukin-6, IL-8 – interleukin-8, M-CSF – macrophage-colony-stimulating factor, LDL-C low density lipoprotein, TG- triglycerides, TNF-alpha – tumor necrosis factor-alpha, VLDL-C – very low density lipoprotein

By the mid of the last decade of the previous century statins were shown to significantly reduce cardiovascular events (1). Shortly after that statins became the first line drugs for treatment of hypertension, diabetes and other significant risk factors for cardiovascular disease (2–12). Actually, the decrease of mortality and morbidity in cardiovascular patients has been attributed to drastic reduction in circulating lipids due to HMG-CoA reductase inhibition (1–5, 7–10). However, experimental and clinical studies conducted in recent few years discovered many non-lipid effects of statins. Among those effects, probably the most significant one is the anti-inflammatory effect (13–22). In order to understand better the effects of statins, namely atorvastatin, we will start with description of the underlying mechanisms of atherosclerosis, followed by pharmacology of atorvastatin.

ATHEROGENESIS

The novelties in experimental and clinical research have shown that atherosclerosis is by no means inevitable degenerative result of ageing, accompanied by the „silent" atheroma, but a long-term chronic disorder characterized by accumulation of fat and fibrous connective tissue in the middle and large arteries size, accompanied by local and systemic inflammatory reaction (14, 23).

Atherogenesis starts by accumulation of the lipids within the intima, followed by fatty and fibrous proliferation, resulting in bulging into the arterial lumen. Such bulging is known as atheroma. Atherom does not produce overt symptoms at first, but as it grows progressively it limits circulation, and depending on its location it can cause cardiac angina, myocardial infarction, stroke, intermittent claudication, renal insufficiency and other clinical syndromes due to narrowing of the arterial lumen.

Atherogenesis lasts for decades and it is believed to have an initial phase, stage of lesion enlargement (progression) and the stage of complication or thrombosis. Atherogenesis may be regarded as „reaction to injurious agents" caused by risk factors or some other harmful agents (14, 17).

It is believed that the process of atherogenesis begins by endothelial dysfunction. The term „endothelial dysfunction" refers to several pathological conditions, such as changes of anti-coagulation and antiinflammatory properties of endothelium, impaired modulation of vascular growth, and disregulation of vascular remodeling (24). However, the existing literature frequently defines endothelial dysfunction as *impaired endothelium-dependent vasorelaxation* induced by the lack of NO inside the blood vessel (25). Under physiological conditions, antioxidative system (firstly: superoxide dismutase) minimizes this reaction and maintains the balance between O_2 and NO (25).

Among many other causes, accelerated and impaired NO degradation by reactive oxygen species have been implicated, most probably, as main causes of endothelial dysfunction. In addition, enzyme systems such as xanthine oxidase, NADH/NADPH oxidase and endothelial nitric oxide synthase are the sources of reactive oxygen species, e. g. oxidant stress, producing endothelial dysfunction, are known to be involved in the pathogenesis of many cardiovascular diseases including hypercholesterolemia, atherosclerosis, diabetes and heart failure (25)

MECHANISM OF LESION FORMATION IN ATHEROSCLEROSIS

In normal conditions leucocytes are not bound to the blood vessel endothelium. However, in case of endothelial dysfunction, such as in the initial stage of atherosclerosis, the earliest morphological change visible is binding, i. e. adherence of monocytes and T lymphocytes, but not granulocytes, to blood vessel endothelium. Monocytes do not remain bound to endothelium but pass through and enter into the subendothelium and intima. Monocytes are accumulated within intima and, after limited multiplication, transform into foam cells. The cytokine M-CSF stimulates proliferation and differentiation of macrophages, as well as the expression of the scavenger receptors. Foam cells die out and their lipid content makes the necrotic part of the lesion. Fibrous wrapping or fibrous cap forms around that middle part. Lipid content also includes stimulated smooth muscle cells originating form the media of arterial wall. These are *initial* changes. New monocytes enter such lesion and get transformed in macrophages. All that is accompanied by further proliferation and production of the extra-cellular matrix and accumulation of extra-cellular lipids. Activated macrophages, T lymphocytes and smooth muscle cells generate additional mediators, such as adhesive molecules, cytokines, chemokines, and growth factors that induce further growth of the lesions. This is a *progression* phase (14, 16, 22). Accumulated macrophages inside the atheroma produce enzymes (metaloproteinases) that degrade the collagen, which protect the fibrous cap. Interferon gamma, produced by T lymphocytes also decomposes the fibrous cap. The rupture may occur as the fibrous cap is getting thinner due to the action of proinflammatory cytokines. The last stage of atherogenesis is when after the rupture, the content of atheroma (cholesterol, macrophages, tissue factors, necrotic debris, thromboxane A2, 5-hydroxytriptamine, adenosine diphosphate and platelet activating factor) reaches the blood inducing *thrombosis*. This is the underlying mechanism of coronary and cerebral thrombosis. On the other hand, stability of atherosclerotic lesions may be influenced by the calcification of the intima (13 -18, 22).

LIPOPROTEINS

Lipoproteins are particles with cholesteryl esters and triglycerides inside the hydrophobic center. Nonesterified cholesterol, phospholipids, and apoproteins are positioned around such central part. Some lipoproteins also contain two forms of protein B (large molecular mass): form B48 (produced in the intestines and found in chylomicrons), and B100 (synthesized in liver and found in VLDL-C, IDL-C and LDL-C). This outer layer is rather hydrophilic and proteins inside this layer are known as *apolipoproteins*.

Lipoproteins vary regarding the relation of central lipids, size and density of particles. The density of particles is defined by ultracentrifugation, and depending on their density as:

- Chylomicrons
- HDL-C
- LDL-C
- IDL-C
- VLDL-C

LDL-C represent a heterogeneous group divided into three subgroups: light and large particles density 1.02–1.03 g/ml, intermediary size particles density 1.03–1.04 g/ml and the small dense with density 1.04–1.06 g/ml (26). There are two sub-populations of IDL-C: IDL-I (32 nm particles) and IDL-II (26 nm particles) (27). There are also two subgroups of VLDL-C: large and light TG-rich VLDLD-1 (Sf 60–400) and small, dense CE -rich VLDEL-2 (Sf 20–60) (28).

DYSLIPIDEMIAS

Dyslipidemias may be primary and secondary. Primary ones are genetically determined, and classified in six phenotypes according to Frederickson. Criteria for classification are fractions of increased lipoproteins.

Frederickson classification has no diagnostic but prognostic and therapeutic implications. The patients with dyslipidemia type IIa suffer from the highest risk of ishemic heart disease. This type of dyslipidemia is known as familiar hypercholesterolemia, and is the result of monogenic defect of LDL-C receptors. Frederickson classification is presented in the table 1.

Table 1. Frederickson/WHO classification of dyslipidemias (hyperlipoproteinemias).

TYPE	Elevated lipoproteins	Cholesterol	Triglycerides	Atherosclerosis risk	Medications
I	Chylomicrons	+	+++	Not elevated	None
IIa	LDL-C	++	Not elevated	High	Inhibitors of HMG-Co A reductase and raisins
IIb	LDL-C+VLDL-C	++	++	High	Derivatives of fibric acid inhibition of HMG-Co A reductase, nicotinic acid.
III	Beta-VLDL-C	++	++	Moderate	Derivatives of fibric acid
IV	VLDL-C	+	++	Moderate	Derivatives of fibric acid
V	Chylomicrons+VLDL-C	+	+	Not elevated	None

HMG-Co A, 3-hydroxy-3-methylglutary-coenzyme A; LDL-C, low density lipoproteins; VLDL-C, very low density lipoproteins; beta VLDL-C, qualitatively abnormal form of VLDL-C; +, elevated levels.

Secondary dyslipidemias are the consequence of:

- diabetes mellitus
- alcoholism
- nephrotic syndrome
- chronic renal insufficiency
- liver disorders, and
- drugs (antagonists of beta adrenergic receptors, thiazide diuretics, estrogens and isotretionine)

EFFECTS OF LIPOPROTEINS

HDL-C acts highly anti-atherogenic. This is explained by removing cholesterol i. e. LDL-C from the periphery, and inhibition of oxidation of lipoproteins. Namely, HDL-C particles transport also serum esterases, such as acetylhydrolase and paraoxonase that decompose biologically active oxidized phospholipids, and thus neutralize their pro-inflammatory action (14, 16, 29).

Native LDL-C is not atherogenic. In fact, „modified" LDL-C, including oxidation, lipolysis, proteolyisis and aggregation is taken up by macrophages and generate foam-cells. „Modified" lipids induce the expression of adhesive molecules, chemokines, pro-inflammatory cytokines and inlammatory mediators and contribute for and maintain the inflammation (14, 16, 30, 31). As far as LDL-C subfractions are concerned the greatest atherogenic potential have small and very dense LDL-C lipoproteins (32).

VLDL-C and IDL-C possess significant atherogenic strength. These lipoproteins, as well as LDL-C act atherosclerotically only in oxidized form (modified form) (17). There are some data demonstrating that beta-VLDL-C can also activate the inflammation inside arterial endothelium (17, 33).

LIPIDS AND ATHEROSCLEROSIS (OXIDATION HYPOTHESIS)

According to the oxidation hypothesis the basic risk factors inducing atherosclerosis are increased concentration of LDL-C, VLDL-C or both.

Atherosclerosis begins by aggregation of LDL-C within subendothelium. Serum levels of LDL-C define this aggregation. Aggregation takes place at predisposed sites (reaction of the blood vessel wall to altered hemodynamics). LDL-C diffuses through the junction of endothelial cells, and the aggregation depends on interaction between the apolipoprotein B and proteoglycans from the matrix. Macrophages cannot take up native LDL-C. According to the oxidation hypothesis, LDL-C aggregated within the intima, which is partially bound to proteoglycans, enter in oxidized form the macrophages that subsequently become foam cells. Lipooxygenases represent the most significant source of reactive oxygen species, i. e. oxidant stress necessary for oxidation of LDL-C. Modified products of LDL-C, include also oxidized LDL-C, induce expression of adhesion molecules, chemokines, and proinflammatory cytokines. Such modified/oxidized LDL-C take part in inflammatory process of atherosclerosis (13, 14, 16, 17, 22, 30, 31).

However, it is believed that oxidation hypothesis of human atherosclerosis has not yet been fully ascertained for two reasons: first, chemical analysis demonstrated that types of human lipids and proteins extracted from

human atheromas did not always match with products of lipoproteins oxidized *in vitro* (17). Secondly, clinical findings show that therapy with antioxidants such as vitamins, does neither affect nor improve the outcome of cardiovascular events in humans (17, 35).

LIPOPROTEIN MARKERS IN ATEROSCLEROSIS

Lipoprotein markers of atherosclerosis represent increase of serum concentrations:

- LDL-C
- LDL-C
- VLDL-C
- total cholesterol
- triglyceride

INFLAMMATION AND ATHEROSCLEROSIS

Virchow (36) described atherosclerosis as inflammation almost 150 years ago. Inflammatory component of atherosclerosis has been accepted only recently.

Inflammation in atherosclerosis has both local and systemic component (13–17, 22, 37). Intimal infiltration with macrophages and T lymphocytes is the pathological substrate of local inflammation and the beginning of atherosclerosis (13–17, 22, 37). Simultaneous stimulation of smooth muscles of the arterial wall continues to spread local inflammatory process. Activated macrophages, T lymphocytes, and smooth muscles promote local generation of additional inflammatory mediators, such as adhesive molecules, cytokines, chemokines, and growth factors. Inflammatory cytokines generating macrophages and T lymphocytes modify endothelial function, smooth muscle proliferation, collagen breakdown, and thrombosis. On the other hand, growth factors produced by cells of inflammatory infiltrate stimulate proliferation of smooth muscles that accumulate inside atheroma and stimulate growth and progression of atheromatous process. Finally, rupture of atheroma resulting in thrombosis, occurs in three fourths of patients. Therefore, the inflammatory process is present in all stages of atherogenesis: at the beginning, during progression, and in thrombosis (13–17, 22, 37).

As mentioned before, macrophages, T lymphocytes and stimulated smooth muscle cells, promote the production of proinflammatory and procoagulant cytokines. The cytokines may act in nearly cell/s („paracrine") bind to its own receptor/s („autocrine-response"), through direct cell contact („juxtacrine- response") and on remote target organs via the blood („endocrine-response"). Local inflammatory process within the arterial wall stimulates the production of primary proinflammmatory cytokines (IL-1, TNF alpha) which further recruit inflammatory cells into the vascular tissue. Some proinflammatory cytokines, such as IL-6 not only participate in local inflammatory process, but also become messenger cytokines while passing in the blood, and affect distant target organs. IL-6 causes acute protein phase reaction in the liver, thus producing CRP, serum amiloid A, soluble intercellular adhesion molecul-1, macrophage inhibitor cytokine -1, sP-selectine, and CD 40 ligand (22). In addition to IL-1 and THF alpha,

CRP stimulates expression of cellular adhesion molecules thus mediating the adhesion of leucocytes to the vascular endothelium (37, 38). Cytokine IL-6 increases concentration of fibrinogen and the plasminogen activator type-1 inhibitor (39, 40). All these changes indicate systemic inflammation, no wonder atherosclerosis is considered a systemic inflammatory disorder (22).

Central clinical significance in systemic inflammation belongs to CRP, which directly affects the process of atherogenesis. The most significant among these direct effects are the following (17, 41–43):

- ability to bind and activate the complement
- induce expression of several adhesion molecules
- induce expression of tissue factors
- stimulation of LDL-C intake inside the endothelial macrophages
- aggregation of monocytes inside the arterial wall
- stimulation of the production of monocytic chemo-attracting protein-1.

In addition, it should be mentioned that increase in concentration of IL-6 and CRP is not merely a sign of atherosclerosis, but also a sign of developing type 2 diabetes in individuals expressing no insulin resistance (17, 44).

INFLAMMATION MARKERS ON ATHEROSCLEROSIS

There are local and systemic inflammation markers in atherosclerosis.

Local inflammation markers are:

- increase of atheroma temperature from 0.2/0.3°C to 2.2°C comparing with unchanged intima
- increased production of heat in atherom. It was detected by infra red optical fibers
- alteration of atheroma pH. Metabolic activity (lactates) and increased temperature of atheroma reduce pH thus making the atheroma more acidous
- alteration of atheroma volume and the intima-media thickness. These changes were discovered using imaging techniques (MRI) and computed tomography. Although there is a correlation between changes of atheroma temperature and pH, and process of atherosclerosis, these parameters should be verified in future clinical studies.

Systemic markers of inflammation are:

- CRP
- Interleukins (IL-6 and IL-8)
- Serum amiloid A
- Soluble intercellular adhesive molecule-1 and
- TNF-alpha.

The CRP is the most important from the clinical standpoint, and for the following reasons (17, 45, 46):

- long half-life
- no circadian variations
- high sensitivity assays commercially are available providing comparable results in fresh, stored and frozen plasma and
- values < 1 represent low, from 1 to 3 moderate, and finally > 3 mg/l high cardiovascular risk (22).

ATORVASTATIN (LIPITOR®, SORTIS®)
Chemical and physical properties

Atorvastatin is a synthetic compound with heptanoic acid in the side chain, thus being a synthetic analog of the intermediary product of 3-hydroxy-3methylglutaryl-coenzyme A. From the chemical standpoint, atorvastatin is calcium-trihydrate(3:1)[R-(R*,R*)]-2-(4-fluorophenyl)-beta, delta-dihydroxy-5-(methyl-ethyl)-3-[phenyl-4-(phenylamino)carbonyl)]-1H-pyrrole-1-heptanoic acid, with the following structural formula (figure 1):
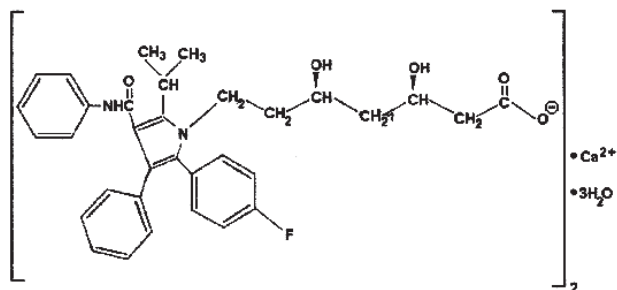

Figure 1. Structural formula of atorvastatin (calcium-trihydrate(3:1)[R-(R*,R*)]-2-(4-fluorophenyl)-beta, delta-dihydroxy-5-(methyl-ethyl)-3-[phenyl-4-(phenylamino)carbonyl)]-1H-pyrrole-1-heptanoic acid.

Empiric formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2 \cdot Ca_3H_2O$, molecular mass 1209,42.

Effects

There are two basic effects of atorvastatin (15, 18–21, 47, 52–55):
- on lipoprotein complex metabolism and
- non-lipid (pleiotropic).

Lipoprotein complex
- reduces total cholesterol, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and triglycerides, and produces variable increase of HDL and apolipoprotein A-1,
- also lowers total cholesterol, LDL-C, VLDL-C, apo B, triglycerides and non HDL-C, simultaneously increasing HDL-C in patients with isolated hypertriglyceridemia, and
- decreases LDL-C in patients with dysbetalipoproteinemia.

Non-lipid (pleiotropic) effects
These are antiinflammatory and related effects.
The antiinflammatory effects affect the following:
- blood vessels endothelium
- local inflammatory infiltration
- atheroma stability
- coagulation
- thrombocytes
- vasculogenesis and
- immune mechanisms.

Among other effects, there is an effect on bone formation.

Mechanism of action

A number of clinical studies demonstrated with great certainty that increase in total cholesterol and LDL-C was connected with increased risk for atherosclerosis and cardiovascular disease (48–51, 75, 76). Such a risk has been significantly reduced by reducing total cholesterol and LDL-C. Mechanism of such reduction is explained in the following way:
- atorvastatin, like other statins, is a selective and competitive inhibitor of HMG-CoA reductase. This enzyme converts 3-hydroxy-3-methylglutaryl-conzyme A to mevalonate, a precursor of sterols, including cholesterol. Such inhibition of cholesterol in liver results in lowering total cholesterol in serum
- reduced cholesterol level in the liver cells activates the process that increases the number (expression) of hepatic LDL-C receptors. Those receptors in the liver take up LDL-C from blood, and thus reduce serum levels of LDL-C (52, 53)
- decreases of LDL-C serum levels is also the result of eliminating the LDL-C precursors (VLDL-C and IDL-C) and the decreased hepatic synthesis of VLDL-C (54)
- atorvastatin, like other statins, reduces serum triglycerides levels by the similar mechanisms (55)
- statins, including atorvastatin, reduce the level of lipids and oxidized LDL-C in atheromas (15, 56).

Antiinflammatory effect of statins, including atorvastatin has been well documented and usually preceding the decrease in serum cholesterol and LDL-C levels. Mechanisms of such action are:
- reduced production (expression) of endotheline-1, a powerful vasoconstriction and mytogenic agent, and stimulation of upregulation of endothelial NO synthesis, i. e. increased bioavailability of NO within the vascular endothelial cells (57). In experimental model of atherosclerosis in rabbits, atorvastatin inhibits expression of monocyte chemoattractant protein-1. This is a cytokine affecting leukocytes, which than migrate from the endothelium into the intima. This reduces the inflammatory infiltrate inside the intima, i. e. reduces inflammatory process in the arterial intima (58, 59)
- inhibition of proinflammatory cytokines (IL-1, IL-6, TNF-alpha, and gamma-interferon), matrix metalloproteinases, and the proinflammatory enzyme COX-2 in stimulated smooth muscle cells, macrophages and T-lymphocytes occurs simultaneously (20, 21, 58, 59)
- atorvastatin, simvastatin, and fluvastatin inhibit inflammation within the intima of the arterial wall (17, 58), while pravastatin and cerivastatin reduce contents of macrophages within the atherosclerotic plaque (17, 60), as well as the expression of tissue factors and matrix metalloproteinase (17, 61)
- reduction of lipids, macrophages and metalloproteinases results in stabilization of atheromatous plaque (15) and
- among the rest of mechanisms, it is necessary to underline, that atorvastatin reduces activation of platelets and simultaneously stimulates type 3 NO synthase thus reducing platelet aggregation (62).

Atorvastatin and serum inflammatory markers

Statins, including atorvastatin, reduce serum proinflammatory markers (17, 20, 21, 64, 65). It should be emphasized that atorvastatin reduces serum concentration of CRP in patients with hyperlipidemia and proven coronary heart disease even in the lowest therapeutic dose of 10 mg (63). According to Ridker et al. (66) increased concentration of CRP is considered a more reliable parameter comparing to increased LDL-C serum levels regarding the prognosis of the first event.

Clinical examination

Atorvastatin efficacy was studied as a mono therapy, compared with other statins, and as a prevention treatment.

Monotherapy – Atorvastatin has been clinically used since 1997, but the efficacy studies started much earlier. The first efficacy study in patients with primary hypercholesterolemia was published in 1995 (67). LDL-C was increased (>4.14, but <6.21 mmol/l), in these patients (n=81) within triglycerides in the majority of patients were within normal range (<3.39 mmol/l). This was a randomized, double-blind, placebo study. The patients were given atorvastatin in doses of 2.5, 5, 10, 20, 40, and 80 mg/day during 6 weeks. Atorvastatin was demonstrated to reduce dose-dependently LDL-C concentration from 25–61%. Reduction of concentration of total cholesterol and apo B was also dose-dependent. There was however, no significant changes in HDL-C, apo A-1, and Lp(a) concentrations.

The effect of atorvastatin is relatively rapid. Approximately 90% of maximum reduction was achieved by the end of the second week of treatment. Serious undesirable effects were not reported.

Those first clinical results were confirmed by the consecutive studies and extended to sub-fractions of LDL-C. In placebo controlled and non-comparative studies on a relatively small number of patients, it was demonstrated that atorvastatin reduces level of LDL-C, as well as atherogenic subfraction of small, dense LDL-C particles. These studies included patients with primary and mixed hyperlipoproteinemia (Frederickson types II A and IIB) (68–70).

Comparative studies – Several statins were in use at the beginning of the last decade of previous century. The question arose as to which one was the most effective in terms of milligram-equivalent doses and reduction of LDL-C level. Until introduction of atorvastatin in the treatment of hypercholesterolemia, it was demonstrated that pravastatin and simvastatin reduce LDL-C level for 28.5% and 37% respectively, in milligram-equivalent doses of 20 mg/day. The efficacy issue became even more important after introduction of atorvastatin and rosuvastatin. CURVES (2) first, followed by STELLAR (10) study was therefore conducted.

CURVES study (2) included 534 patients with hypercholesterolemia (LDL-C ≥160 mg/dl, or 4.2 mmol/l, and triglycerides ≥400 mg/dl or 4.5 mmol/l) receiving 10, 20, 40, and 80 mg/day of atorvastatin, 10, 20 and

40 mg/day of simvastatin, 10, 20, and 40 mg/day of pravastatin, 20, 40, and 80 mg/day of lovastatin, and 20, and 40 mg/day of fluvastatin. The atorvastatin was demonstrated to be the most efficient. Atorvastatin reduced concentrations of LDL-C significantly more comparing with simvastatin, pravastatin, lovastatin, and fluvastatin (Table 2). Atorvastatin also more significantly lowers total cholesterol levels comparing with simvastatin, pravastatin, lovastatin, and fluvastatin (Table 2). All statins reduce level of triglycerides. However, statistically significant reduction was only achieved with doses of 40 mg/day. On the other hand, there was practically no change in HDL-C level table 2).

Table 2. Changes (percentage) in lipoproteins levels following 8 weeks of treatment with statins in patients with hypercholesterolemia (modified according to Jones P et al., 1998).

Lipoprotein parameters	Atorvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin
LDL-C					
10 mg/day	−38	28**	−19**	–	–
20 mg/day	−46	35**	−24**	−29**	−17**
40 mg/day	−51	41**	−34**	−31**	−23**
80 mg/day	−54	–	–	−48	–
Total Cholesterol					
10 mg/day	−28	21**	−13**	–	–
20 mg/day	−35	26**	−18**	−21**	−13**
40 mg/day	−40	30**	−24**	−23**	−19**
80 mg/day	−42	–	–	−36	–
Triglycerides					
10 mg/day	−13	12	3	–	–
20 mg/day	−20	17	−15	−12	−5
40 mg/day	−32	15**	−10**	−2**	−13**
80 mg/day	−25	–	–	−13	–
HDL-C					
10 mg/day	5.5	6.8	9.9	–	–
20 mg/day	5.1	5.2	3.0	7.3	0.9
40 mg/day	4.8	9.6*	6.2	4.6	−3.0
80 mg/day	−0.1	–	–	8.0	–

*P <0.05 **P<0.01 related to milligram equivalent doses of atorvastatin.

STELLAR (10) study confirmed the results of CURVES (2) study and in addition demonstrated that in patients (n=2431) with hyperlipidemia (LDL-C ≥160mg/dl but <250 mg/dl, and triglycerides ≥400 mg/dl) treated for 6 weeks with atorvastatin in doses of 10, 20, 40, and 80 mg/day reduction of LDL-C levels was more efficient comparing with simvastatin given in doses of 10, 20, 40 and mg/day, or pravastatin in doses of 10, 20, and 40 mg/day, but less efficient comparing to rosuvastatin in doses of 10, 20, 40, and 80 mg/day. The analysis of the results also demonstrated that reduction of LDL-C due to 10 mg/day of rosuvastatin was more significant comparing with 10 mg/day of atorvastatin, but doses of 40 mg/day of each atorvastatin and rosuvastatin made no difference in the extent of reduction LDL-C levels. Rosuvastatin was also more efficient than atorvastatin after 52 weeks of treatment (n=412) with primary hypercholesterolemia (72).

Another parameter for evaluating efficacy of statins is the time necessary to achieve the target reduction of LDL-C levels (73). There have been several such studies. A study on patients (n=318) with documented atherosclerosis, including the myocardial infarction, angina pectoris, stroke, intermittent claudication, and vascular interventions on lower limbs (4). After 54 weeks of treatment with atorvastatin, simvastatin, lovastatin, and fluvastatin

308 patients completed the study. The target value of LDL-C was <100 mg/dl (2.59 mmol/l), although the researchers discontinued treatment at the point when LDL-C value reached <105 mg/dl (2.71 mmol/l). Initial doses of atorvastatin were 10 mg/day, simvastatin 10 mg/day, lovastatin 20 mg/day, and fluvastatin 20 mg/day. After 12 weeks of treatment atorvastatin already reduced LDL-C serum level significantly (p=0.05) more comparing to other statins. However, mean doses of statins after 54 weeks of treatment were 20 mg/day for atorvastatin, 40 mg /day for simvastatin, 80 mg/day for lovastatin, and 40 mg/day of fluvastatin combined with 20 mg/day of colestipol. The target values of LDL-C were by the end of the weak 54 reported in 83% in atorvastatin group, 81% in simvastatin group, 75% in lovastatin group and 50% in fluvastatin group. Atorvastatin achieved the target values of LDL-C for the shortest period of 170 days, while it took fluvastatin almost a year (table 3).

Table 3. Efficacy parameters of statins at the target values of LDL-C (≥100 mg/dl or 2.6 mmol/l) in patients with documented atherosclerosis (modified according to Brown AS et al. 1998).

Parameters	Atorvastatin n=78	Simvastatin n=76	Lovastatin n=78	Fluvastatin n=76
Mean time for achieving the target value of LDL-C	170 days	253 days*	253 days*	344 days*
Mean dose at the end of week 54	20 mg/day	40 mg/day	80 mg/day	40 mg/day and 20 mg/day of colestipol
Percentage of patients with achieved target value of LDL-C	83	81	75	50*

*P < 0.05 related to atorvastatin.

Such comparable studies for rosuvastatin have not been conducted. The most probable reason is this statin toxicity. Rosuvastatin causes rhabdomyolysis even at doses of 10 mg/day, and the unwanted effects are dose-related. There were 18 cases of with rhabdomyolysis since the registration, and the drug was removed from clinical use (74).

Prevention and intensive (aggressive) treatment – The studies regarding the effects of preventive treatment with high doses of atorvastatin (intensive or aggressive treatment) comparing with standard doses of other statins on progression of atherosclerosis, coronary disease and ischemic stroke have been conducted.

It is known that fatal outcomes and recurrent ischemic events are the most frequent in the early period after acute coronary syndrome (75, 76). Therefore the effects of intensive therapy with atorvastatin on the early recurrent events were studied. Atorvastatin was given in dose of 80 mg/day parallel with placebo, and initiated 24–96 on admission (MIRACLE study)(7). The patients (n=3086) had unstable angina and non-Q myocardial infarction. Primary endpoint parameters for assessment of efficacy were mortality, non-fatal myocardial infarction, cardiac arrest, and symptomatic myocardial recurrent ischemia, i. e. conditions requiring emergency hospitalization. Following 16 weeks of treatment atorvastatin re-duced unwanted ischemic events (16%), hospitalization (26%), and ischemic stroke (50%) compared to placebo. Atorvastatin reduced LDL-C concentrations from 124 mg/dl (3.2 mmol/dl) to 72 mg/dl (1.9 mmol/l) (7).

Long-term research of preventive treatment with low doses of atorvastatin (10 mg/day) also demonstrated that atorvastatin significantly (p=0.0001) reduced major cardiovascular events (non-fatal myocardial infarction and fatal coronary heart events). Atorvastatin was administered for 3.3 years (ASCOT-LLA study)(9) to patients with hypertension (164.2/95.0 mmHg) regarded not to be dyslipidemic (total cholesterol level ≥6.5 mmol/l). The results were compared to placebo group also including hypertensive patients deemed not to be dyslipidemic (164.2/95.0 mmHg and total cholesterol level ≥6.5 mmol/l). Atorvastatin group included 5.168, and placebo group 5.137 patients. Primary endpoint efficacy parameters were non-fatal myocardial infarction and total cardiovascular events. After 3.3 years treatment total cardiovascular events (389 vs 486, p= 0.005), total coronary events (178 vs 247; p= 0.005) and fatal and non fatal stroke (89 vs 121; p= 0.024) were significantly lowered. In addition, there was no significant difference (p=0.16) in mortality between atorvastatin and placebo group. Interestingly, atorvastatin lowered total cholesterol by about 1 mmol/l compared with placebo at 12 months and by 1.1 mmol after 3 years of follow up. Difference between male and female patients was insignificant (9).

Clinical studies testing effects of intensive atorvastatin (80 mg/day) treatment comparing with conventional doses of simvastatin (40 mg/day) on progression of atherosclerosis were of particular significance.

The first study (ASAP) demonstrated regression of atherosclerosis due to atorvastatin in doses of 80 mg/day (intensive treatment) in patients with familial hypercholesterolemia (6). Primary endpoint efficacy parameter was the change of the intima-media thickness of the carotid arteries and carotid arteries bifurcation on both sides. Two years of treatment by atorvastatin (80 mg/day) and simvastatin (40 mg/day) resulted in changes of intima-media thickness. The group of patients treated with atorvastatin (n=160) demonstrated significant regression (p=0.0017) i. e. reduction of thickness, while in the group on simvastatin (n=163) the intima-media thickness of carotid arteries increased significantly (p=0.063). Simultaneously, atorvastatin reduced LDL-C levels from 8.0 mmol/l to 3.88 mmol/l, while simvastatin induced reduction from 8.0 mmol/l to 4.1 mmol/l. Based on these results it could be concluded that aggressive treatment with atorvastatin, but not with standard doses of simvastatin, resulted in regression of atherosclerotic (intima media thickness) changes, as measured by quantitative B-mode ultrasound, in patients with familial hypercholesterolemia (6).

It was demonstrated several years later (REVERSAL study) that aggressive but not standard treatment with statins reduces progression of coronary atherosclerosis (12). The participants were the patients with at least one

obstruction and minimum coronary arteries narrowing of 20%. Primary efficacy treatment endpoint was the change in atheroma volume expressed in percents. These patients were treated for 18 months with doses of 80 mg/kg (intensive treatment) of atorvastatin, and 40 mg/day (standard treatment) of pravastatin. At the end of treatment LDL-C level in the atorvastatin group (n=253) was reduced to 79 mg/dl (2.05 mmol/l), and CRP for 36.4%, while in pravastatin group (n=249) the reduction was to 110 mg/dl (2.85 mmol/l) and CRP for 5.2%. Significant progression (p=0.001) of coronary arteries atherosclerosis was reported in pravastatin group. On the other hand, there was no progression of atherosclerosis in atorvastatin group (p=0.98). Beneficial effect of atorvastatin was attributed to significant simultaneous reduction of LDL-C and CRP levels (12).

Greater efficacy of intensive treatment with atorvastatin (80 mg/day) opposite to standard treatment with pravastatin (40 mg/day) regarding prevention of mortality and major cardiovascular events in patients with acute coronary syndrome (acute myocardial infarction and high-risk unstable angina) was also demonstrated in another study. These patients were treated with atorvastatin (n=2099) and parvastatin (n=2063) from 18 to 36 months (medium treatment period was 24 months). Atorvastatin reduced LDL-C levels to 62 mg/dl (1.60 mmol/l), comparing to 95 mg/dl (2.46 mmol/l) with parvastatin. Efficacy of atorvastatin was significantly (p=0.005) higher in prevention of mortality and major cardiovascular events comparing to pravastatin. The conclusion was that all patients had significant benefits from treatment with any of these statins in regard to lowering LDL-C below the target levels (LDL-C <100 mg/dl, or 2.9 mmol/l), but it is still not clear what are the optimal LDL-C levels for treatment of patients with dyslipidemias (11).

The latest clinical studies confirmed that intensive compared to moderate statin therapy in patients with coronary artery disease reduces the rate of progression of atherosclerosis (77, 78). The outcome was significantly related to greater reductions in the levels of both biomarkers atherogenic lipoproteins and CRP (78), whereas in the study of Ridker et al (77) patients who had low CRP levels after statin treatment had better clinical outcomes than those with higher CRP levels regardless the resultant levels of LDL cholesterol. Thus, it is still not clear the mechanism of benefit of statin therapy, although clinicians agree that the levels of both biomarkers should be monitored. Of course, further studies are warranted.

In addition, intensive treatment with atorvastatin (80 mg/day) (after 18 months significantly delayed onset (p=0.03), and reduced the ischemic events for 46% (p=0.048) in comparison to 37% of angioplasty (percutaneous coronary revascularization) group. LDL-C levels in atorvastatin group were reduced to 77 mg/dl (2.0 mmol/l), while in angioplasty group, it was 119 mg/dl (3.0 mmol/l) (5).

Finally, it should be underlined that atorvastatin did not improve the maximal walking time compared to placebo, for intermittent claudication due to peripheral artery disorder. Increase in total cholesterol and LDL-C increases the risk from peripheral arterial disorder and claudication (79), therefore it was anticipated that if efficient for lowering LDL-C it would also be efficient for the treatment of intermittent claudication. After 12 months of treatment atorvastatin in doses of 10 and 80 mg/day significantly reduced total cholesterol, LDL-C, and triglycerides compared to placebo (p=0.001). Nevertheless, atorvastatin did not significantly reduce walking time (treadmill test), although it did alleviate pain-free walking time compared to placebo (80).

Pharmacokinetics

Pharmacokinetics was studied on both adults and the elderly (81, 82). Atorvastatin plasma levels found in the elderly were for approximately 40% higher compared to C_{max}, and the half-life time ($t_{1/2}$) was prolonged compared to younger adults (81).

Absorption - Atorvastatin is rapidly absorbed after oral administration. Maximum blood concentrations occur within 1–2 hours following intake. Bioavailability of atorvastatin is approximately 14%. Blood concentrations of atorvastatin are higher following evening drug administration compared to morning. However, it does not affect the inhibition of HMG-CoA reductase, and it could be administered anytime during the day.

Distribution – 90% of atorvastatin is bound to plasma proteins. Volume of distribution is approximately 381 liters. It passes through the hemato-encephalic barrier and through the placenta.

Metabolism – Atorvastatin is metabolized in the liver by cytochrome P450 3A4, and approximately 70% of inhibitory activity of HMG-CoA reductase is attributed to active circulating metabolites.

Excretion – Atorvastatin and its metabolites are eliminated primarily in the bile, breast milk, and partially in feces. Half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours.

Indications

There are two basic indications: hypercholesterolemia and prevention of cardiovascular disorders.

a) Hypercholesterolemia
- primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia (Frederickson Types IIa and IIb) when diet proves insufficient in lowering total cholesterol, LDL-C, apo B and triglycerides
- as adjunct therapy for patients with elevated triglycerides (Frederickson Type IV),
- treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond to diet
- as an adjunct therapy to diet to lower total cholesterol, LDL-C, and apo B in boys and postmenarchal girls age between 10–17, suffering from heterozygous familial hypercholesterolemia, nonresponding adequately to diet, with LDL-C levels <190 mg/dl,

or ≥160 mg/dl, with a positive familial history of cardiovascular disease together with 2 or 3 risk factors for cardiovascular events.

b) Prevention of the cardiovascular disorder (this indication was approved by the FDA in 2004)

- reducing the risk of myocardial infarction, and
- reducing the risk of revascularization procedures and pectoral angina.

Posology and method of administration

Atorvastatin is given orally in doses of 10, 20, 40, and 80 mg/day.

According to the NCEP ATP III suggestions the target values for LDL-C are (83):

- rational target level of LDL-C in high risk patients is <100 mg/dl (2.6 mmol)
- rational optimal target value for very low LDL-C levels in high risk patients is <70 mg/dl (1.8 mmol)

Lowering the risk of ischemic heart disorders depends on the duration of treatment measured in years. Table 4 presents meta analysis of 58 studies.

Table 4. Reduction in the risk of ischemic heart disease events (95% confidence intervals) for 1 mmol/l decrease in the LDL-C serum level according to the duration of treatment in years (meta analysis with 58 studies – modified according to Law MR et al 2003).

Year of treatment	Risk reduction %
First	11 (4–18)
Second	24 (17–30)
Third-fifth	33 (28–37)
Sixth and subsequent	36 (26–45)

Unwanted effects

Atorvastatin is generally well tolerated and unwanted effects are rarely seen.

Gastrointestinal disorders (constipation in particular), headache, and insomnia are the most frequent undesirable effects.

Elevated hepatic transaminases were described in approximately 1–2% of patients. However, up to three-fold increase is not considered significant. These changes are usually reversible. The transaminases levels should be checked, before initiation of treatment, and thereafter at least once a month during first three months, and in six months afterwards. Active hepatic disorders and alcoholism call for caution.

The most serious unwanted effects caused by all statins, including atorvastatin, are myopathy, myositis, rhabdomyolysis, and renal failure. Treatment with atorvastatin should be discontinued when the creatine phosphokinase is multi-fold increased (more than 10 times basal values), and there are also signs of myopathy. There is increased risk of rhabdomyolysis when the statins, including atorvastatin are combined with fibric acid derivatives, nicotinic acid, and cyclosporines.

Law et al. (84) reported 42 fatal outcomes due to rhabdomyolysis in patients treated with statins in the USA since the first statin was registered in 1987 and until the year 2003.

On the other hand, for 7 moths following the registration of rosuvastatin (July 2003 – FDA document) 11 fatal outcomes due to rhabdomyolysis have been registered in USA alone (74).

Contraindications

Atorvastatin is contraindicated in patients with:

- active liver disease (persistent elevation of serum transaminases), pregnancy and lactation.
- hypersensitivity to any component of the drug.

Interactions

The risk of myopathy during treatment is increased with concurrent administration of:

- cyclosporine
- fibric acid derivatives
- nicotinic acid
- erythromycin
- itraconazole, ketoconazole
- antiviral drugs (protease inhibitors), and
- oral contraceptives.

Atorvastatin increases plasma digoxin concentrations for approximately 20%. On the other hand, antacids reduce atorvastatin plasma concentrations for approximately 35%.

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