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OLD AND NEW IN LIPID LOWERING THERAPY: FOCUS ON THE EMERGING DRUGS

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Abstract

The link between cholesterol and atherosclerosis has been long known. Studies on HDL (high density lipoprotein) cholesterol showed that it has two important roles: one in the transport of cholesterol and another directly on vascular endothelium, with a protective action and potential anti-atherogenic effects. Statins are the most common lipid-lowering drugs. Other drugs used in the treatment dyslipidemia are bile acid sequestrants, nicotinic acid, ezetimibe, probucol, neomycin, and fibrates. Because the response to treatment is not always satisfactory, new classes of drugs with different mechanisms of action have been developed in the latest years.

Rezumat

Legătura dintre colesterol și ateroscleroză este de mult timp cunoscută. Studiile efectuate asupra HDL-colesterolului (*high density lipoprotein*) au arătat două roluri importante: unul asupra transportului de colesterol și altul direct asupra endoteliului vascular, având o acțiune protectoare și cu efecte potențial anti-aterogene. Statinele sunt cele mai cunoscute medicamente hipolipemiente. Alte categorii de medicamente folosite în tratamentul dislipidemiilor sunt: secheștrantii de acizi biliari, acidul nicotinic, ezetimib, probucol, neomicina, fibratii. Deoarece răspunsul la tratament nu este totdeauna satisfăcător, în ultimii ani au fost introduse în terapie noi clase de medicamente hipolipemiente, cu mecanisme de acțiune diferite față de cele cunoscute până acum.

Keywords: dislipidemia, new lipid lowering drugs.

Introduction

In 1910, the German researchers have drawn attention to the link between cholesterol and atherosclerosis. Forty years later, John Gofman from the University of California found that high levels of HDL (high density lipoprotein) are associated with a reduced risk of coronary heart disease [16]. Subsequently, in 1977 the Framingham Study revealed that a low level of HDL can be an independent predictive factor of coronary heart disease [17]. Based on these observations, the present study had the objective to clarify the metabolic and antiatherogenic role of HDL, and therapeutic strategies to influence its level.

HDL is a lipoprotein; plasma lipoproteins are complexes of lipids and proteins, excepting free cholesterol, which are formed by a combination of esters of cholesterol, triglycerides and phospholipids. Lipoproteins are classified according to their density and migration properties in the electrophoretic field as: HDL, LDL, VLDL, IDL and chylomicrons having the role of blood conveyers for cholesterol and triglycerides [7].

HDL is composed of a core made up of cholesterol esters and triglycerides that is surrounded by phospholipids and specialized proteins called apolipoproteins. The latter would be intended to solubilize and to carry lipids in plasma. Recently the role of apolipoproteins in the metabolic process of the lipids at enzymatic level or at the cell-surface receptors has been described [8]. The two major parts of the particle of HDL are: apolipoprotein A-1, synthesized in the liver and intestine and apolipoprotein A-II, synthesized in the liver [20, 21].

Apolipoprotein A-1 is produced by the liver and takes up the cholesterol and phospholipids from the liver and peripheral cells (including macrophages) using the ABCA 1 (ATP-binding cassette transporter 1) transporter, forming the disc-shaped HDL particles [20].

Free cholesterol from the disc-shaped HDL is converted to cholesterol ester by lecithin-cholesterol acyltransferase (LCAT) – which in turn leads to the formation of the spherical HDL particles.

The mature HDL particles can be reshaped into small size particles through the release of apolipoprotein A-1 due to the action of hepatic or endothelial lipase, which hydrolyzes triglycerides and phospholipids of the HDL complex [20]. HDL cholesterol ester can be transferred to the LDL/VLDL by a cholesterol transfer protein (CETP-cholesteryl ester transfer protein) and then taken over by the hepatocyte from a specific LDL receptor through the process of endocytosis [12]. HDL cholesterol ester and free cholesterol can also be transferred directly to the hepatocyte by a specific receptor SR-BI (scavenger receptor class B type I). The hepatic cholesterol can be processed again and taken on by the ABCA 1 (ATP-binding cassette transporter 1) or secreted in the bile as free cholesterol or bile acids or may be included in particles of lipoproteins and secreted again into circulation (Fig. 1, 2, 3).

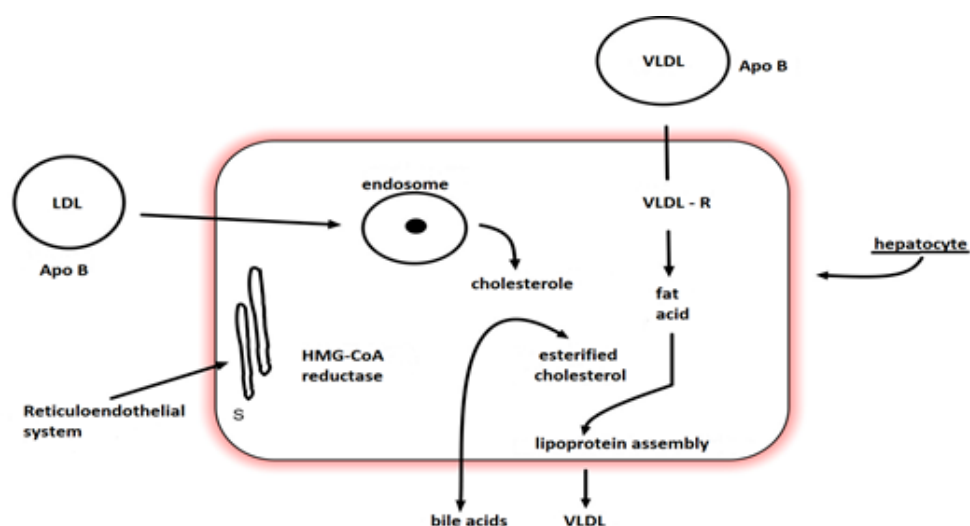


Figure 3.
The metabolism of hepatic cholesterol

Legend: HMG-CoA = hydroxymethylglutaryl coenzyme A reductase

Studies on HDL cholesterol have shown that it has two important roles: one in the cholesterol transport and another directly on the vascular endothelium, having a protective action, with potential anti-atherogenic effects (endothelial antiapoptotic effect, antiinflammatory effect, antithrombotic effect, potentiating the nitric oxide synthesis or stimulation of the endothelium restoration process) [12, 15, 16].

Another important element in lipid metabolism is CETP (cholesteryl ester transfer protein) [12]. Circulating CETP mediates the transfer of esterified cholesterol from the particle of HDL to LDL and VLDL lipoproteins, rich in triglycerides. At the same time, triglycerides are transported in the opposite direction. As a result of this process, HDL cholesterol decreases, the VLDL cholesterol content increases and the particles of LDL become smaller and denser.

Framingham Heart Study drew attention on the implication of HDL cholesterol level in assessing the risk of myocardial infarction [17]. Subsequently, LIPID and CARE studies showed that a low level of HDL cholesterol is a negative predictive factor of cardiovascular events [36, 42].

Moreover, a meta-analysis of 26 studies published in 2010 by Baigent et al. outlined the importance of reducing LDL cholesterol and decreasing the incidence of heart disease and ischemic stroke [4].

Due to the clinical implications of reducing the cholesterol levels, the guidelines of both the American and the European Society of Cardiology recommend a reduction in LDL cholesterol values according to SCORE system. Patients with low cardiovascular risk will maintain LDL cholesterol at 140 mg/dL, those with average risk at 100 mg/dL and those at high risk will need to reduce LDL cholesterol to 70 mg/dL. In cases where such therapeutic targets cannot be achieved, it is recommended to reduce LDL cholesterol by at least 50% of the initial value, or up to the level at which adverse effects occur.

This can be achieved by using one or more drugs from several classes of therapeutic drugs that act at different levels of the cholesterol metabolic cycle.

Statins reduce production of VLDL and are associated with a post-treatment decrease in enzymatic activity recovery of HMG-CoA reductase. Statins also increase LDL receptor activity, due to intrahepatic decrease of cholesterol availability. Moreover, statins decrease the production of VLDL and are associated with a post-treatment reduction in enzymatic activity recovery of HMG-CoA reductase.

The available statins are: pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin as well as pitavastatin, which is available only in some countries. They are the most potent drugs for lowering LDL cholesterol. For some statins, like simvastatin (40-80 mg/day) or atorvastatin (20-40 mg/day), it was also found an increase in the level of HDL cholesterol and the concentration of apolipoprotein A-1. Atorvastatin and rosuvastatin decrease the triglycerides levels, with this effect being dose-dependent [4].

The most common side effects of statins are: hepatic dysfunction (they increase the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), muscle pain (myalgia, rhabdomyolysis with inflammation of muscles or even acute renal failure due to myoglobinuria), renal dysfunction (proteinuria by inhibition of tubular active transport of the small protein molecules), increasing the risk of diabetes mellitus in patients treated with high-doses of statins. Sometimes the statin therapy may be associated with depression, sleep disorders, memory loss or sexual dysfunction [35].

The bile acid sequestrants are substances able to block the intestinal reabsorption of bile acids, with a reduction of the level of intrahepatic cholesterol. They also increase LDL receptor activity, increase circulatory LDL-cholesterol clearance and induce a minimal increase in HDL-cholesterol by enabling the intestinal formation of native HDL.

In this category there are included: cholestyramine, colestipol and colesevelam [39]. These medications are administered in patients with moderate increase of LDL-cholesterol in a recommended dose of 8 g/day for cholestyramine, 10 g/day for colestipol and 1.5-4.5 g/day for colesevelam [39].

The bile acid sequestrants may be administered in combination with statins, having a synergistic action of lowering LDL cholesterol and increasing HDL cholesterol.

The use of these medications is limited by the gastrointestinal side effects: nausea, abdominal pain, and bloating. They can augment liver enzymes levels and may hinder the absorption of some medicines like digoxin, warfarin or fat-soluble vitamins.

Nicotinic acid (niacin) inhibits the hepatic VLDL production and as a consequence, it inhibits also the metabolism of LDL. Furthermore, it increases the level of HDL cholesterol by reducing lipid transfer of cholesterol from HDL to VLDL and delays HDL clearance.

In the AIM-HIGH study, the combination of statins with niacin has been used in patients with cardio-vascular disease and low levels of HDL cholesterol and elevated triglycerides. The study was stopped because of the increased number of brain ischemic injury in patients treated with niacin [41].

The results of other studies are expected to show whether niacin brings additional advantages or not in lowering LDL cholesterol and raising HDL cholesterol. Niacin dosage varies between 1-3 g/day. The formula has a poor tolerability, conducting to flush in 80% of patients, itching, paraesthesia and nausea [41].

Other important issues related to the administration of nicotinic acid are represented by the fact that it increases blood sugar levels, induces hyperuricemia and may precipitate an acute attack of gout. Moreover, it can produce hypotension, especially in patients treated concomitantly with vasodilators.

Ezetimibe is the first representative of a class of cholesterol-absorption inhibitors that acts at the surface of the intestinal mucosa, without affecting the absorption of triglycerides and fat-soluble vitamins [40]. It interferes with Niemann-Pick C1-like 1 (NPC1L1) protein responsible for transluminal cholesterol transport [3, 24]. Ezetimibe reduces the absorption of cholesterol and thus the amount of cholesterol taken up by the liver is reduced. The daily dose is 10 mg [40].

The precise role of ezetimibe compared with other lipid-lowering drugs is unclear. It seems that the same effect of reducing LDL cholesterol

can be achieved by simply increasing the dose of statins. Transaminases level increases if administered in combination with statins.

Probucol has also the property of inhibiting cholesterol absorption. It has a weak action of reducing LDL cholesterol and stronger action of increasing HDL cholesterol levels [31]. Probucol favors reabsorption of skin xanthomas in the familial hypercholesterolemias [44]. The recommended dose is 500 mg twice a day and its side effects are angioedema, QT prolongation and eosinophilia. However, in patients with peripheral atherosclerosis its clinical utility has not been proven.

Neomycin acts by forming an insoluble complex with bile acids; thus it reduces the lipids level through a mechanism similar to the bile acid sequestrants. It is also designed to inhibit the secretion of apolipoprotein A on the surface of the hepatocyte [26]. It may be indicated in patients with familial hypercholesterolemia and excess of lipoprotein A. Recommended dose: 1 g twice a day. The common side effects reported were nephrotoxicity and ototoxicity.

Fibrates have the major effect of lowering serum triglycerides in a percentage of 35-50% and to moderately increase of HDL cholesterol [6, 14, 34]. This effect is mediated at least in part by activating PPARs (peroxisome proliferator-activated receptors), a transcription factor from the hepatocyte core [38].

A meta-analysis of 18 trials with fibrates showed that although they are active on lipid metabolism, they do not influence general or cardiovascular mortality and slightly increase the non-vascular cause of mortality [22]. Gemfibrozil, fenofibrate and bezafibrate are the most used fibrates.

Gemfibrozil, used in a dose of 600 mg twice a day, increases the level of HDL-cholesterol. The Helsinki Heart Study showed the effectiveness of gemfibrozil in patients with hypertriglyceridemia and high cardiovascular risk [13].

Fenofibrate is used for reducing triglycerides in patients with type IV or V of hyperlipoproteinemia. It is used as capsules of 200 mg or a formula with nanocrystales with 145 mg/capsule. Two studies on fenofibrate in the diabetic patients, FIELD and ACCORD, showed that it has a beneficial effect on the microcirculation, reducing the progression of diabetic retinopathy [2, 30].

Bezafibrate can be administered at a dose of 200 mg three times a day. It has predominantly renal elimination, so doses will be reduced in patients with renal insufficiency according to creatinine clearance [25, 27].

Fibrates can cause side effects as: muscle toxicity and an increase in serum creatinine. They also interfere with the metabolism of warfarin, which requires a dose reduction by about 30% in order to prevent the effects of anticoagulant over dosage and bleeding complications.

Although lipid-lowering drugs are numerous and diverse, there are still cases in which even by using their combinations, effective control of cholesterol levels and its fractions cannot be achieved, which leads to a remaining high risk of cardiovascular events. This finding has been a challenge for researchers, which has led to the emergence and development of new classes of drugs with different mechanisms of action beside those known up until now.

Emerging lipid lowering therapies

Inhibitors of LDL cholesterol secretion. It is known that triglyceride microsomal transfer protein (MTP) plays an important role in the formation of apolipoprotein B present in the hepatocytes and enterocytes. Inhibition of MTP reduces the secretion of VLDL cholesterol, lowering cholesterol and triglycerides levels [7]. Lomitapide[®] is an oral inhibitor of MTP, which showed in clinical trials a significant decrease in LDL cholesterol and apolipoprotein B, up to 55% [10]. Its effect is limited by the fact that during therapy aminotransferases values can raise to values up to 5 - 11 times higher, and that the amount of fat in the liver can be increased [10].

Agents that alter the production of LDL cholesterol. Apolipoprotein B is essential for the production of VLDL cholesterol (precursor of LDL cholesterol) and cholesterol clearance. Mipomersen is a direct inhibitor of apolipoprotein B synthesis, whose administration is associated with a reduction in LDL cholesterol by more than 37 percent [29]. Noted side effects were mostly injection site reaction, flu symptoms and increases in aminotransferases levels.

Agents affecting LDL cholesterol catabolism. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme involved in the degradation of the LDL receptor [1]. It has been noted that in populations with PCSK9 mutations, these are associated with low levels of LDL cholesterol and therefore with a low risk of coronary artery disease (Figure 4). Several strategies to decrease PCSK9 activity have been used, the most effective being the use of monoclonal antibodies (anti-PCSK9) [18]. This complex is in phase II clinical trial. First preliminary studies show a decrease in LDL cholesterol levels and a dose-dependent action on apolipoprotein B1.

The monoclonal antibody SAR236553/REGN727 pairs with PCSK9 preventing its fixation on the LDL particle and thus the intracellular cycle is not altered [18].

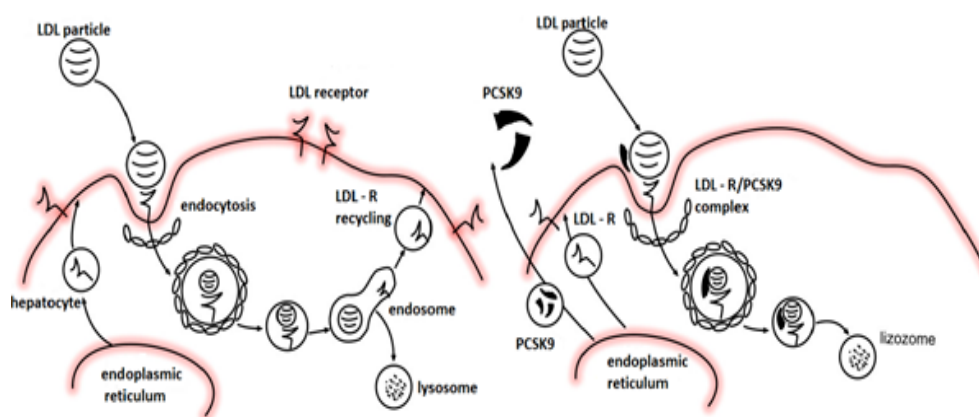


Figure 4.

Schematic display of LDL-receptor function (on the left) and the interaction with PCSK9 (right) [23, adapted]

The AMG 145 Study used PCSK9 monoclonal antibodies in doses of 150 to 300 mg, once every two weeks. The lowering of LDL cholesterol levels was up to 75% [11]. Because this monoclonal antibody has no liver passage it will not produce hepatic adverse reactions, one of the most common problems with the clinically used lipid lowering drugs.

Another study in progress is LAPLACE-TIMI 57 which investigates the effectiveness and tolerability of PCSK9 monoclonal antibody associated with statins in hypercholesterolemic patients. The years to come will show us how important are these additional therapies in lowering LDL cholesterol.

Agents that increase HDL cholesterol. HDL cholesterol clears cholesterol from the peripheral tissues, transports it to the liver where it is either degraded or recycled. This process is called reverse cholesterol transport and is favored by the enzyme – CETP (cholesterol ester transfer protein). As such, the inhibition of this enzyme increases the level of HDL cholesterol.

Torcetrapib is the first CETP inhibitor agent which was studied in the Illuminate trial, which included 15,000 patients treated with atorvastatin [5]. It has been observed a decrease in LDL cholesterol by 25% and a significant increase in HDL cholesterol (72%). However, the study was stopped because of increased mortality. Moreover, an increase in plasma sodium, a decrease in potassium and an increase of blood pressure values were also reported [5].

Dalcetrapib, another CETP inhibitor, was studied in patients with recent acute coronary syndrome. Although dalcetrapib significantly

increased HDL cholesterol compared to *placebo*, the study was stopped early because there were no significant differences between groups regarding the risk of cardiovascular events [37].

Anacetrapib has a significant effect of raising HDL cholesterol levels without increasing blood pressure like torcetrapib. It was studied in the DEFINE trial on a relatively small number of patients with coronary artery disease [9], and currently a big study - HPS3-TIMI 53- is in progress.

Evacetrapib, administered alone, 100 mg per day, increases HDL in variable proportions from 54% to 130% and lowers LDL cholesterol with 14 – 36% in a dose-dependent manner [28]. ACCELERATE Study, which is in progress, will be able to show whether this drug is effective and safe for routine clinical use.

Other emerging therapies

Thyroid mimetics, which have selective affinity for the thyroid hormone receptor β , expressed in the liver. Eprotirome-analogue of the thyroid hormones can decrease LDL-cholesterol levels in a dose-dependent way [25]. However, in order to be recommended as hypolipidemic treatment further studies are needed.

Estrogen hormone replacement therapy has been shown to have lipid-lowering effect: it reduces LDL cholesterol and increases HDL cholesterol as well as triglycerides [43], although the cardiovascular protective effect has not been confirmed. Tamoxifen, an anti-estrogen, seems to reduce LDL cholesterol level without changing the amount of HDL cholesterol or triglycerides. However, it did not show cardiovascular benefits [19].

Conclusions

Summarizing, the development of new, effective and risk-free lipid lowering therapies is mandatory as the present resources are not always successful in lowering LDL cholesterol which in turn exposes the patient at an increased risk of major vascular events. Moreover, long-term administration of statins, the most widely used class of lipid lowering drugs can expose patients to several important risks, such as increasing the incidence of new cases of diabetes, polyneuropathy, depression, memory disorders and in a very small percentage interstitial pulmonary diseases [4].

As such, the quest for the perfect lipid lowering drug is still ongoing and the coming years will certainly bring new means of managing the burden of dyslipidaemia.

References

1. Abifadel M., Rabes J.P., Devillers M., Munnich A., Erlich D., Junien C., Mutations and polymorphisms in the proprotein convertase subtilizing kexin 9 (PCSK9) gene in cholesterol metabolism and disease. *Hum Mutat*, 2009; 30: 520-529.
2. ACCORD Study Group, ACCORD Eye Study Group, Chew E.Y., Effects of medical therapies on retinopathy progression in type 2 diabetes. *N. Engl. J. Med.*, 2010; 363: 233.
3. Altmann S.W., Davis H.R.Jr., Zhu L.J., Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science*, 2004; 303: 1201.
4. Baigent C., Blackwell L., Emberson J., Holland L.E., Reith C., Bhalra N., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*, 2010; 376: 1670-1681.
5. Barter P.J., Caulfield M., Eriksson M., Effects of torcetrapib in patients at high risk for coronary events. *N. Engl. J. Med.*, 2007; 357: 2109.
6. Birjmohun R.S., Hutten B.A., Kastelein J.J., Stroes E.S., Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J. Am. Coll. Cardiol.*, 2005; 45: 185.
7. Blasiole D.A., Davis R.A., Attie A.D., The physiological and molecular regulation of lipoprotein assembly and secretion. *Mol. Biosyst.*, 2007; 3: 608-619.
8. Breslow J.L., Familial disorders of high-density lipoprotein metabolism. In: Scriver C.R., Beaudet A.L., Sly W.S., Valle D., eds. *The Metabolic and Molecular Bases of Inherited Disease*. 7th ed. New York: McGraw-Hill; 1995: 2031-2052.
9. Cannon C.P., Shah S., Dansky H.M., Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N. Engl. J. Med.*, 2010; 363: 2406.
10. Cuchel M., Bloedon L.T., Szapary P.O., Kolansky D.M., Wolfe M.L., Sarkis A., Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N. Engl. J. Med.*, 2007; 356: 148-156.
11. Dias C., Shaywitz A., Smith B., Emery M., Bing G., Gibbs J., A phase 1, randomized double-blind, placebo-controlled, ascending single dose study to evaluate the safety, tolerability and pharmacodynamics of AMG145. *Circulation*, 2011; 124: Abstract 10701.
12. Eisenberg S., High-density lipoprotein metabolism. *J. Lipid. Res.*, 1984; 25: 1017-1058.
13. Frick M.H., Elo O., Haapa K., Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N. Engl. J. Med.*, 1987; 317: 1237.
14. Fruchart J.C., Brewer H.B. Jr., Leitersdorf E., Consensus for the use of fibrates in the treatment of dyslipoproteinemia and coronary heart disease. Fibrate Consensus Group. *Am. J. Cardiol.*, 1998; 81: 912.
15. Drăghici I., Aramă C., Nedelcu A., Monciu C.M., Stănescu M., Tuchiță C., Development of a new LC method for the identification, separation and assay of simvastatin and its impurities. *Farmacia*, 2013; 61(2): 229-239.
16. Gofman J.W., Delalla O., Flazier F., Freeman N.K., Lindgren F.T., Nichols A.V., The serum lipoprotein transport system in health, metabolic disorders, atherosclerosis and coronary heart disease. [Reprint of a 1956 Plasma paper]. *J. Clin. Lipidol.*, 2007; 1: 104-141.
17. Gordon T., Castelli W.P., Hjortland M.C., Kannel W.B., Dawber T.R., High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am. J. Med.*, 1977; 62: 707-714.
18. Graham M.J., Lemonidis K.M., Whipple C.P., Subramaniam A., Monia B.P., Crooke S.T., Antisense inhibition of proprotein convertase subtilisin/kexin type 9 reduces serum LDL in hyperglycemic mice. *J. Lipid. Res.*, 2007; 48: 763-767.
19. Grey A.B., Stapleton J.P., Evans M.C., Reid I.R., The effect of the anti-estrogen tamoxifen on cardiovascular risk factors in normal postmenopausal women. *J. Clin. Endocrinol. Metab.*, 1995; 80: 3191.

20. Havel R.J., Kane J.P., Introduction: structure and metabolism of plasma lipoproteins. In: Scriver CR, Beaudet A.L., Sly W.S., Valle D., eds. *The Metabolic and Molecular Bases of Inherited Disease*. 7th ed. New York: McGraw-Hill; 1995: 1841-1851.
21. Hussain M.M., Zannis V.I., Intracellular modification of human apolipoprotein AII (apoAII) and sites of apoAII synthesis: comparison of apoAII with apoCII and apoCII isoproteins. *Biochemistry*, 1990; 29: 209-217.
22. Jun M., Foote C., Lv J., Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*, 2010; 375: 1875.
23. Kees G.H., Davidson M.H., Kastelein J.P., Diagnosis and treatment of familial hypercholesterolemia. *Eur. Heart. J.*, 2013; 34: 962-971.
24. Rizea G.D., Mihele D., Manea Ș., Ionescu D., Rădană Vila, The determination of hypolipemiant activity of a new vegetal natural food supplement to animals with induced hyperlipemia. *Farmacia*, 2013; 61(2): 411-419.
25. Ladenson P.W., Kristensen J.D., Ridgway E.C., Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N. Engl. J. Med.*, 2010; 362: 906.
26. Lanford R.E., Estlack L., White A.L., Neomycin inhibits secretion of apolipoprotein [a] by increasing retention on the hepatocyte cell surface. *J. Lipid. Res.*, 1996; 37: 2055.
27. Monk J.P., Todd P.A., Bezafibrate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hyperlipidaemia. *Drugs*, 1987; 33: 539.
28. Nicholls S.J., Brewer H.B., Kastelein J.J., Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. *JAMA*, 2011; 306: 2099.
29. Raal F.J., Santos R.D., Blom D.J., Marais A.D., Charng M.J., Cromwell W.C., Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Lancet*, 2010; 375: 998-1006.
30. Rajamani K., Colman P.G., Li L.P., Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet*, 2009; 373: 1780.
31. Reaven P.D., Parthasarathy S., Beltz W.F., Witztum J.L., Effect of probucol dosage on plasma lipid and lipoprotein levels and on the protection of low density lipoprotein against *in vitro* oxidation in humans. *Arterioscler. Thromb.*, 1992; 12: 318.
32. Reda A., HDL-Cholesterol Metabolism. www.cardiolipid.com.
33. Rosenson R.S., Brewer H.B. Jr., Davidson S.W., Cholesterol efflux and Atheroprotection. Advancing the Concept of Reverse Cholesterol Transport. *Circulation*, 2012; 125: 1905.
34. Rosenson R.S., Wolff D.A., Huskin A.L., Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. *Diabetes Care*, 2007; 30: 1945.
35. Rusu E., Jinga M., Rusu F., Statin therapy in patients with diabetes and hepatitis C. *Farmacia*, 2013; 61(6): 1204 – 1215.
36. Sacks F.M., Pfeffer M.A., Moye L.A., The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N. Engl. J. Med.*, 1996; 335: 1001-1009.
37. Schwartz G.G., Olsson A.G., Abt M., Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N. Engl. J. Med.*, 2012; 367: 2089.
38. Staels B., Dallongeville J., Auwerx J., Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*, 1998; 98: 2088.
39. Steinmetz K.L., Colesevelam hydrochloride. *Am. J. Health. Syst. Pharm.*, 2002; 59(10): 932-939.
40. Sudhop T., Lutjohann D., Kodal A., Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation*, 2002; 106: 1943.
41. The AIM-HIGH Investigators, Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N. Engl. J. Med.*, 2011; 365: 2255-2267.

42. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. *N. Engl. J. Med.*, 1998; 339: 1349-1357.
43. The Writing Group for the PEPI Trial, Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*, 1995; 273: 199.
44. Yamamoto A., Matsuzawa Y., Yokoyama S., Effects of probucol on xanthomas regression in familial hypercholesterolemia. *Am. J. Cardiol.*, 1986; 57: 29H.

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