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**New compounds able to control hepatic cholesterol metabolism: Is it possible to avoid statin treatment in aged people?**

**Trapani L *et al*.** Hypocholesterolemic treatment in elderly

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**Abstract**

Aging is characterized by the loss of homeostasis that leads to changes in the biochemical composition of tissues, reduced ability to respond adaptively to environmental stimuli, and increased susceptibility and vulnerability to diseases including coronary artery diseases, carotid artery disease, and brain vessel disease. Hypercholesterolemia is one of the primary risk factors for these pathologies, whose incidence is highly related to aging. Almost 25% of men and 42% of women older than 65 years have a serum total cholesterol level greater than 240 mg/dL. The mechanisms behind this age-related increase in plasma cholesterol are still incompletely understood, thus, the control of plasma cholesterol content in aged people is more challenging than in adults. In this review the different pharmacological approaches to reduce plasma cholesterol levels, particularly in aged people, will be discussed. In brief, current therapies are mostly based on the prescription of statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) that are pretty effective but that exert several side effects. More attention should be given to potential drug interactions, potential age-related changes in drug pharmacokinetics, adverse effects such as myopathy and competing risks when statins are prescribed to old patients. In combination or in alternative to statin therapy, other agents might be required to reduce low density lipoprotein (LDL) cholesterol levels. Among the available drugs, the most commonly prescribed are those addressed to reduce cholesterol absorption, to modulate lipoprotein lipase activity and bile acid sequestrants: even these pharmacological interventions are not exempt from side effects. The use of antioxidants or organoselenium compoundsand the discovery of new proteins able to modulate exclusively LDL receptor recycling such as PCSK9 and SEC24 offer new pharmacological approaches to selectively reduce the main causes of dyslipidemia.

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**Key words:** Aging; Cholesterol; Hypercholesterolemia

**Core tip:** The strategies used to reduce plasma cholesterol levels in elderly people are mainly addressed to the inhibition of the rate limiting enzyme of cholesterol biosynthetic pathway, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), in order to increase low density lipoprotein (LDL) receptor membrane exposure and LDL clearance from the circulation. Indeed current therapies are mostly based on the prescription of statins (HMGR inhibitors) that are pretty effective but that exert side effects. More attention should be given to potential drug interactions, potential age-related changes in drug pharmacokinetics, adverse effects such as myopathy and competing risks when statins are prescribed to elderly. Thus, new therapeutic agents should be taken into account.

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**INTRODUCTION**

Aging is characterized by the loss of homeostasis that leads to changes in the biochemical composition of tissues, reduced ability to respond adaptively to environmental stimuli, and increased susceptibility and vulnerability to diseases including coronary artery, carotid artery, and brain vessel diseases[1-3].

Hypercholesterolemia is one of the primary risk factors for these pathologies, whose incidence is highly related to aging. Almost 25% of men and 42% of women older than 65 years have a serum total cholesterol level greater than 240 mg/dL[4]. The mechanisms behind this age-related increase in plasma cholesterol are still incompletely understood. Of particular interest are the findings that indicate a gradual decline in the fractional clearance of low density lipoprotein (LDL) from the circulation[5-7] and a reduced expression of hepatic LDL receptor (LDLr) with increasing age in some species[8,9]. Experimental data show that aging significantly rises secretion rates of biliary lipids (bile salt, cholesterol and phospholipid), and bile cholesterol content as well as sizes and hydrophobicity indices of the bile salt pool[10]. The age-related disruption of cholesterol metabolism could be caused by the progressive decline and perturbation in homeostasis maintenance that occur in aging[11].

Cholesterol biosynthesis is a tightly regulated metabolic pathway that employs multiple feedback mechanisms to maintain homeostasis*.* Over the past several decades, much work has focused on the regulation of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), which catalyzes the conversion of HMG-CoA to mevalonate (MVA) through a four-electron oxidoreduction. This reaction is the rate-limiting step in the synthesis of cholesterol and other isoprenoids such as dolichol, ubiquinone, and prenyls[12].

HMGR is highly regulated. Short-term regulation is achieved by phosphorylation/dephosphorylation reactions exerted by AMP-activated kinase (AMPK) and protein phosphatase 2A (PP2A), respectively. Long-term regulation concerns the modulation of HMGR protein levels by several factors, among others Sterol Regulatory Element Binding Protein (SREBP) and Insulin- induced genes (Insigs), which can affect enzyme transcription, degradation and cholesterol uptake by LDLr as a function of an intracellular sterol amount[13].

**CHOLESTEROL HOMEOSTASIS REGULATION DURING AGING**

Experimental studies on aged rats revealed an increased plasma cholesterol and a sustained hepatic cholesterol biosynthesis, with a full activation of HMGR which results to be completely dephosphorylated[14]. The mechanisms underlying this dysregulation appear to be gender-dependent.

In aged-male rats, the full activation of HMGR observed in aging has been associated with a rise in reactive oxygen species (ROS)[15]. The proposed model is that high ROS levels induce both p38 and AMPK activation. In turn, p38 causes an increased association between PP2A and HMGR, leading to HMGR dephosphorylation and full activation. AMPK phosphorylating activity on HMGR is impaired by the enhanced association of PP2A and HMGR. H2O2-treatment confirms that the effect induced by ROS on HMGR dephosphorylation is mediated by the activation of the p38/MAPK pathway in HepG2 cell line[16].

On the contrary, studies performed on estropausal rats, in which estrogen levels are decreased, suggest that the menopause-related increase in HMGR activity is caused by the decreased activation of AMPK observed upon estrogen deficiency[17,18].

HMGR is an attractive target for the treatment of hypercholesterolemia. Indeed a decrease of intracellular cholesterol synthesis leads to a homeostatic response which induces the up-regulation of cell-surface receptors that bind atherogenic lipoproteins such as LDL and VLDL. The reduction of plasma lipoproteins accounts for the clinical utility of HMGR inhibitors, such as statins. Despite their worldwide use and their beneficial effects, statins can cause myopathy characterized by weakness, pain, elevated serum creatine phosphokinase (CK) and, to a lesser extent, rhabdomyolysis, which is a life-threatening condition[19] Elderly patients are especially vulnerable to side effects of statins: this issue as well as the lack of certainty about their efficacy in aging, can affect the prescription of these medications.

Indeed the Heart Protection Study, PROSPER, and SAGE illustrate the benefit of statin treatment on coronary or surrogate end points in higher-risk elderly patients, although the data is still somewhat controversial, particularly for individuals ≥ 80 years of age. An observational study of acute-care hospitals in the United States identified no association between statin use at discharge and improved survival rate in acute myocardial infarction patients ≥ 80 years of age, although it did find benefit in patients < 80 years of age[20].

Thus an optimal management of cholesterol should take into account the mechanisms at the root of cholesterol metabolism disruption in elderly people, the risk-benefit ratio of statin use and the effects exerted by alternative medications prescribed to reduce hypercholesterolemia. These different pharmacological approaches will be examined in the review.

**INHIBITORS OF CHOLESTEROL SYNTHESIS:**

***Statins***

Statins inhibit competitively HMGR activity impairing HMG-CoA binding. The bulky hydrophobic statins occupy the HMG-binding pocket and part of the CoA cleft[21]. On HMGR inhibition, statins reduce intracellular hepatic cholesterol biosynthesis and decrease intracellular cholesterol accumulation. The reduction of the intracellular cholesterol levels stimulates, *via* SREBP activation, the synthesis of LDLr and their expression on the cell surface. These receptors are responsible for the uptake of LDL and of their precursors, the very LDLs (VLDL) and VLDL remnants, whose hydrolysis produces LDL. The effect of statins on VLDL also explains their role in reducing triglyceride levels[22]. Moreover, hyperlipidemic patients show an increase of Na+/Li+ countertransport activity which is rescued by statin treatment[23-25]. As mentioned above, although the statin therapy is generally well tolerated, the most frequent adverse effect is represented by myopathy. To avoid statin side effects, studies have been performed on genetic polymorphisms that can change statin tolerance and afficacy[25-28].

Statin-associated myopathy is characterized by a broad spectrum of symptoms, ranging from benign myalgia up to life-threatening rhabdomyolysis[22], a syndrome characterized by massive muscle necrosis, with the subsequent release of potassium and other ions into the plasma compartment, and severe myoglobinuria, which may cause damages to kidneys and other organs. Rhabdomyolysis may be accompanied by arrhythmias, acute renal failure, and cardiac arrest. These side effects could be ascribable to statins themselves or to the inhibition of some HMGR end products such as prenyls and ubiquinone[29,30].

In order to avoid statin side effects that older people are more likely to develop, new compounds have been tested to reduce cholesterol synthesis through the inhibition of enzymes (squalene synthase, squalene epoxidase, and oxidosqualene cyclase) downstream the farnesyl pyrophosphate branch point of cholesterol biosynthetic pathway[19]. Nevertheless no compounds have yet entered clinical trials.

**ANTIOXIDANTS**

ω***-3 fatty acids***

Martini and coworkers demonstrated that a diet supplemented with ω-3 fatty acids completely prevents the age-related hypercholesterolemia in 24-mo old rats by exerting a powerful antioxidant activity: the reduction of intracellular ROS content due to the supplementation of ω-3 fatty acids totally prevented the activation of p38/MAPK responsible for PP2A association with HMGR and the consequent activation of the enzyme. The proper HMGR activation state promotes plasma cholesterol maintenance at physiological levels by completely preventing age-related hypercholesterolemia[16,31].

***Resveratrol***

Resveratrol (*trans*-3,5,4´-trihydroxystilbene) is a naturally occurring polyphenol present in red wine and berries[32]. *In vivo* studies have revealed that red wine polyphenols are able to inhibit atherosclerotic progression. Cho and co-workers demonstrated that resveratrol reduces cholesterol synthesis inhibiting both the activity of hepatic HMGR similarly to atorvastatin, and the expression of HMGR mRNA[33].

***Flavoinoids***

Flavonoids are ubiquitous compounds, occurring in various plants and their derivatives such as tea, herbs, citrus fruits and red wine; many of them have been shown to be strong free radical scavengers and antioxidants. Several epidemiological studies have supported the hypothesis that the antioxidant actions of flavonoids may reduce the risk of developing cardiovascular diseases[34].

Punithavati and Prince reported a significant increase in the activity of HMGR in plasma and liver of isoproterenol treated rats. The increased lipid peroxidation induced by the treatment, enhanced the activity of HMGR, which in turn led to an excessive production and accumulation of cholesterol. Pre-treatment with the flavonoids quercetin and α-tocopherol (vitamin E) normalized the activity of HMGR. Thus, the observed decrease in HMGR after quercetin and α-tocopherol administration in rats might be due to the inhibition of lipid peroxidation[35].

Naringenin is the aglycone of naringin, a naturally occurring flavanone glycoside obtained from citrus fruits and grapefruit. Naringenin hypocholesterolemic effect is due to the reduction of both HMGR and acyl CoA: cholesterol O-acyltransferase (ACAT) acitvities[36].

Discovery of isoflavones as HMGR inhibitors in soy food is very intriguing. Kinetic studies showed that isoflavones inhibit HMGR by binding the enzyme active site. Therefore isoflavones may exert steric hindrance between HMGR and its substrates through hydrophobic interactions[37].

***Tocochromanols***

Tocochromanols are a group of amphipathic, lipid-soluble organic molecules composed of a polar moiety derived from tyrosine and a hydrophobic polyprenyl side chain originating from the isoprenoid pathway. Tocochromanols with a phytyl-derived side chain are termed tocopherols whereas those with a geranylgeranyl derived side chain are termed tocotrienols. Some studies clearly demonstrate that tocotrienols are able to inhibit HMGR activity in guinea pigs and chickens. Moreover γ and δ tocotrienols stimulate HMGR ubiquitination and degradation and inhibit SREBP processing[38,39].

***Coumarins***

Coumarins are an elite class of oxygen heterocycles that show a wide variety of biological effects. They are present in many plants, fungi and bacteria and have found for centuries application in the traditional medicine[40]. Coumarins are extremely variable in structure; their biological activities are influenced by the various types of substitutions in their basic structure which consists of fused benzene and α-pyrone rings. Coumarins and their derivatives have attracted intense interest in recent years because of their diverse pharmacological properties: many coumarin derivatives have the special ability to scavenge reactive oxygen species (ROS) and to influence processes involving free radical injury. In particular both esculetin and a novel synthetic 4-methylcoumarin, 4-methylesculetin (ESC), possess two hydroxyl moieties on their benzene rings, and these were the two most effective radical scavengers among the coumarins selected for a structure-activity relationship study in cell culture[41]. Beyond its antioxidant activity, ESC is able to lower HMGR activity reducing PP2A protein levels leading to HMGR hyperphosphorylation. ESC was demonstrated to lower HMGR protein levels through reduced transcriptional and increased degradational events in HepG2 cells[42].

***Organoselenium compounds: Diphenyl diselenide’s case***

Besides enhancing memory in a menopause model in rats[43,44] and decreasing the depressive-like behavior in ovariectomized mice submitted to subchronic stress[43], diphenyl diselenide [(PhSe)2], an organoselenium compound, has been reported to reduce hypercholesterolemia in cholesterol-fed rabbits[45] and in hyperlipidemic Triton WR-1339-induced mice[46]. Moreover, (PhSe)2 was shown to inhibit human LDL oxidation *in vitro*[45], to reduce foam atherosclerotic lesion in hypercholesterolemic LDL receptor knockout (*LDLr -/-*) mice, to decrease infiltration of inflammatory cells in vessel-wall, and to prevent the upregulation of the proatherogenic monocyte chemoattractant protein-1[47]. Recent results demonstrated that (PhSe)2 is able to increase HMGR phosphorylation/inactivation and LDLr protein levels without directly inhibiting HMGR activity[1].

The lack of any evidence in literature about the potential side effects of antioxidant compounds in elderly people, and the abundance of data highlighting their beneficial effects on ROS production and, as a consequence on lipid profile, make the above mentioned compounds eligible for therapeutical interventions addressed to inhibit the mechanisms underlying hypercholesterolemia in the elderly.

**INHIBITORS OF CHOLESTEROL ABSORPTION: FOCUS ON EZETIMIBE**

An alternative approach to the inhibition of cholesterol biosynthesis consists on the limitation of cholesterol absorption: to this aim the compound ezetimide was and is currently used in treatments against hypercholesterolemia.

Ezetimibe, or 1-(4-fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)-hydroxyprophyl]-(4S)-(4-hydroxyphenyl)-(2-azetidinone), inhibits intestinal cholesterol absorption by selectively blocking in the jejunal brush border the Niemann–Pick C1-like 1 protein (NPC1L1), the human sterol transport protein that was expressed at the enterocyte/gut lumen (apical) as well as in the hepatobiliary (canalicular) interface[48]. Current evidence points to the NPC1L1 protein working in conjunction with the adaptor protein 2 (AP2) complex and clathrin to facilitate internalization of free cholesterol into the enterocyte. Cholesterol in the gut lumen or bile incorporates into the cell membrane, where it can bind to NPC1L1. The NPC1L1/cholesterol complex is internalized or endocytosed by joining to AP2 clathrin, creating a vesicle complex that then translocates with the help of myosin along microfilaments in the cytosol to a storage endosome called the endocytic recycling compartment. When intracellular cholesterol becomes low, NPC1L1 is released from the endocytic recycling compartment and traffics back along microfilaments to the cell membrane[49].

A meta-analysis of eight randomized placebo controlled trials showed that monotherapy with ezetimibe in hypercholesterolemic subjects was associated with a significant reduction of LDL-cholesterol (LDL-C), of total cholesterol, of triglycerides, and with an increase of HDL compared to placebo[50].

In terms of elevations in liver function tests, ezetimibe appears to cause similar elevations in transaminases as compared to placebo when given as monotherapy. Also, as combination therapy with statins, ezetimibe does not significantly cause an increase in liver enzymes more than it is observed with statin therapy alone. The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated creatine kinase levels and was not associated to an increased risk of myositis beyond what is noted intreatment with statin alone[51]. Ezetimibe is well tolerated also by elderly individuals and no substantial differences have been observed between young and old people in the drug effects[52]. Among the inhibitors of cholesterol absorption is worth mentioning Orlistat which is prescribed in obese patients improving plasma lipid profile[53]. No studies have been performed on elderly people treated with orlistat [54].

**NIACIN**

Nicotinic acid and nicotinamide (collectively termed niacin) serve as precursors of co-enzymes nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate (NAD+ and NADP+) and are water-soluble vitamins of the vitamin B complex. Niacin was one of the first drugs used to treat hyperlipidemia[55].

Several clinical trials have demonstrated that niacin administration, either alone or combined with other lipid lowering agents, significantly reduces total mortality and coronary events, retards progression, and induces regression of coronary atherosclerosis. Following administration, niacin rapidly inhibits adipocyte lipolysis apparently through the inhibition of hepatic diacylglycerol acyltransferase 2: it leads to the inhibition of triglyceride synthesis and to the decrease of apolipoprotein B-containing lipoproteins; this is accompanied by a similarly rapid drop in plasma levels of free fatty acids[56]. The net effect is a reduced catabolism of HDL and a decreased accumulation of cholesterol esters in LDL particles. It has also been suggested that niacin may directly inhibit the uptake and catabolism of apolipoprotein AI-containing HDL particles, thus acting to further increase plasma levels of HDL[56].

The main problem with the use of niacin is connected to its side effects: administration of pharmacological doses of niacin is accompanied by unwanted effects, primarily a cutaneous reaction called flushing, which occurs in up to 90% of patients. Niacin-induced flushing is mediated primarily by the production of prostaglandins D2 and E2 by dermal/epidermal immune cells, leading to vasodilation of blood vessels and resulting in the symptoms of redness, warmth, tingling and itching[56]. Several gastrointestinal adverse effects, such as nausea, vomiting, dyspepsia and abdominal pain, can also occur. Moreover, the most severe niacin-induced side effect is hepatotoxicity, which is accom­panied by an increase in hepatic transaminase levels[11].

Despite evidence for an atheroprotective effect of niacin from previous small clinical studies, the large outcome trials, AIM-HIGH and HPS2-THRIVE did not reveal additional beneficial effects of niacin on top of statin treatment[57]. Thus the administration of this medication especially in elderly people would deserve more attention.

**FIBRATES**

Fibrates have been used in clinical practice for about half century due to their ability to substantially decrease triglyceride levels and increase HDL, less effects are exerted as LDL lowering agents. All fibrates are peroxisome proliferators-activated receptors (PPARs)α agonists. Fibrates enhance the oxidation of fatty acids (FA) in liver and muscle and reduce the rate of hepatic lipogenesis, thereby decreasing the secretion of very-low-density lipoprotein (VLDL) The increased uptake of triglyceride-derived fatty acids in muscle cells results from an increase in lipoprotein lipase (LPL) activity in adjacent capillaries and a decrease in the amount of apolipoprotein CIII (Apo CIII), which is transcriptionally mediated by PPARα. The decrease in apolipoprotein CIII reduces the inhibition of LPL activity. The enhanced catabolism of VLDL generates surface remnants, which are transferred to HDL. HDL concentrations are further augmented by an increase in PPARα - mediated transcription of apolipoprotein AI (Apo AI) and apolipoprotein AII (Apo AII). Ultimately, the rate of HDL-mediated reverse cholesterol transport may increase[58]. Although the beneficial effects of fibrates, their use is associated with a slightly increased risk (< 0.0%) for myopathy, cholelithiasis, and venous thrombosis[59]. A study in which a subgroup analysis by age was performed showed a significant decrease in total cardiovascular disease events in patients aged < 5 years, but not in patients aged ≥ 5 years. Furthermore, in a study of 1568 men with lower extremity arterial disease, bezafibrate had no significant effects on cardiovascular events in patients aged ≥ 5 years, compared with placebo[60].

**APOB100 ANTISENSE OLIGONUCLEOTIDES**

The recent development of antisense oligonucleotides (ASOs) that can target a specific mRNA and suppress the translation of its protein in the liver has opened up a novel therapeutic window for reducing levels of atherogenic lipoproteins. Mipomersen (ISIS 301012) an antisense inhibitor directed to human apoB-100, was recently documented in phase 2 clinical trials to lower plasma apoB-100 and LDL cholesterol levels in humans. The side effects exerted by ASOs are mainly associated to transaminase[61]. No studies have been performed to understand if differences exist in the efficacy or in the side-effects exerted by these molecules in adults and aged people.

**BILE ACID SEQUESTRANTS**

Bile acids are amphiphilic molecules synthesized from cholesterol in the liver; in their transit through the intestinal lumen they emulsify diet fats, aiding in their absorption. Bile acids are then reabsorbed by active ileal uptake and recycled through the enterohepatic circulation. Bile acid sequestrants, such as colestipol, colestyramine and colesevelam, are anion exchange resins being similar in mechanism of binding bile acids in the intestinal lumen.

They interrupt enterohepatic circulation of cholesterol-rich bile acids and increase their fecal excretion, leading to the depletion of intrahepatic cholesterol, which causes LDLr upregulation[62]. Hepatic LDL uptake is thereby raised, resulting in augmented LDL particle clearance and in the reduction of plasma LDL-C by 15% around. However, the side effects of gastrointestinal intolerance including bloating, abdominal pain and constipation, as well as the inhibition of the absorption of medications like levothyroxine or warfarin, reduce patient compliance. Therefore, bile acid sequestrants are often prescribed with other lipid-regulating agents, most commonly statins[63]. None overall differences in safety or effectiveness of bile acid sequestrant administration between aged and young subjects were observed[52].

**INHIBITION OF PCSK9**

PCSK9, proprotein convertase subtilisin kexin 9, is a 72-kDa protease, highly expressed in the liver[64]. nce secreted, PCSK9 binds LDLr inducing the redistribution of the receptor from the cell surface to lysosomes: indeed PCSK9 appears to change the itinerary of the LDLr, diverting internalized LDLr to degradation in lysosomes and preventing them from recycling to the cell surface[64].

PCSK9 inhibition is considered an attractive target for therapy against hypercholesterolemia. The current drug approaches tested to pharmacologically inhibit PCSK9 in humans are mainly focused on gene silencing that targets both PCSK9 intra- and extra-cellular functions, and on mimetic peptides and monoclonal antibodies that exclusively target circulating PCSK9 and therefore its extracellular function. Other approaches such as orally active cell permeable small molecules that target PCSK9 processing have not reached preclinical development[65]. The subcutaneous administration of the PCSK9 antisense oligonucleotide (ASO) produced by different pharmaceutical companies led to an increase of LDLr hepatic expression and to a concomitant reduction in circulating total cholesterol levels in mice[66] and in non-human primates[67]. Peptides mimicking the EGFA domain of the LDLr interacting with PCSK9 at the plasma membrane have also been developed to inhibit PCSK9 function. A synthetic EGFA peptide reduced in a dose-dependent manner the cellular degradation of the LDLr induced by exogenously added recombinant PCSK9[68]. Duff *et al*[69] were able to reverse the PCSK9 mediated effect on cell surface LDLr by using antibodies that recognize epitopes on PCSK9 in the vicinity of the region within the catalytic domain interacting with the LDLr. Evaluation of treatments over the long term will determine whether the beneficial effects of PCSK9 inhibition on LDL-C levels will directly translate into coronary artery disease risk reduction[71,72].

Chen *et al*[72] identified PCSK9 as a specific SEC24A-dependent COPII cargo: indeed as trans-membrane and soluble proteins co-translationally inserted into the ER, it is packaged into transport vesicles coated with COPII (coat protein complex II) for the export from the ER and the delivery to the Golgi for further processing[73].

Chen *et al*[72] reported that complete deficiency of SEC24A is compatible with normal development and survival in mice. However, these animals exhibit markedly reduced plasma cholesterol and increased hepatic LDLr levels due to selective blockade in the secretion of PCSK9. Consistent with these genetic data, hepatic LDLr levels are up-regulated in SEC24A defi­cient mice as a consequence of a specific depend­ence of PCSK9 on SEC24A for efficient exit from the ER.

The loss of SEC24A disrupts PCSK9 secretion without affecting other COPII-dependent processes such as SREBP activation. PCSK9 represents the first example of a soluble vertebrate cargo that is differentially regulated by specific interaction with selective components of the COPII machinery. Although complete deficiency of SEC24A in mice is compatible with embryonic devel­opment or survival to adulthood, no human patients have yet been identified with genetic deficiencies in any of the four SEC24 paralogous genes. The SEC24A-deficient phenotype suggests a potential role for genetic variation at the SEC24A locus in the control of plasma cholesterol in humans, a key determinant of risk for myocardial infarction and stroke.

Complete deficiency of SEC24A is compatible with survival and normal development in mice, suggesting that pharmacologic inhi­bition of hepatic SEC24A expression/function to achieve reduction in plasma cholesterol may be well tolerated as a potential approach to inhibit PCSK9 secretion[72].

**CONCLUSION**

Atherosclerosis is the major cause of heart disease, stroke, and death during aging in both developed and developing countries, for which the rise of lipid levels into the bloodstream represents a primary risk factor. Epidemiological data have indicated that dyslipidemia and coagulation disturbances are among the most remarkable functional alterations leading to the development of atherosclerotic condition.

Oxidative stress has recently been involved in the pathogenesis of several diseases such as atherosclerosis. The production of free radicals has been found to be a major causative factor for the peroxidative damage to plasma lipoprotein which are responsible for the initiation and progression of atherosclerosis in hyperlipidemic subjects[13]. Both the conditions predisposing to artery diseases occur in the elderly which is defined as the series of the deteriorative changes occurring during the adult period of life that underlie increased vulnerability to challenges and decreased survival[12].

The strategies used to reduce plasma cholesterol levels in elderly people are mainly addressed to the inhibition of the rate limiting enzyme of cholesterol biosynthetic pathway, HMGR, in order to increase LDLr membrane exposure and LDL clearance from the circulation. Indeed current therapies are mostly based on the prescription of statins (HMGR inhibitors) that are pretty effective but that exert several side effects. More attention should be given to potential drug interactions, potential age-related changes in drug pharmacokinetics, adverse effects such as myopathy and competing risks when statins are prescribed to old patients. In combination or in alternative to statin therapy, other agents might be required to reduce LDL-C levels. Among the available drugs, the most commonly prescribed are those addressed to reduce cholesterol absorption, to modulate lipoprotein lipase activity and bile acid sequestrants: even these pharmacological interventions are not exempt from side effects. As an example, the efficacy, safety, and tolerability of a nutraceutical-based protocol (containing berberine 500 mg, policosanol 10 mg, red yeast rice 200 mg, folic acid 0.2 mg, coenzyme Q10 2.0 mg, and astaxanthin 0.5 mg) in elderly hypercholesterolemic patients previously intolerant to statins have been recently demonstrated[74].

The use of antioxidants or organoselenium compounds(PhSe)2and the discovery of new proteins able to modulate exclusively LDLr recycling such as PCSK9 and SEC24 offer new pharmacological approaches to selectively reduce the main causes of dyslipidemia. In order to be effective, pharmacological interventions should be aimed at deleting the causes of hypercholesterolemia considering their age and gender dependence. Indeed, very few research studies are dedicated to elderly (Table 1).

Thus, the selectivity of the different pharmacological targets according to the causes at the root of the pathology could increase the risk/benefit ratio of the prescribed medications. If on one hand elderly people entered epidemiological studies assessing the tolerability and the effectiveness of drugs in this physiological condition, on the other hand researches aimed at evaluating the efficacy of medications in women, and in particular in elderly women are still missing. Thus further studies aimed at evaluating the putative efficacy and safety of the therapeutic approaches in alternative to statin treatment to lower hypercholesterolemia and in turn artery disease risks in elderly people are needed.

**REFERENCES**

1 **da Rocha JT**, Trapani L, Segatto M, La Rosa P, Nogueira CW, Zeni G, Pallottini V. Molecular effects of diphenyl diselenide on cholesterol and glucose cell metabolism. *Curr Med Chem* 2013; **20**: 4426-4434 [PMID: 23590714]

2 **Kotsaftis P**, Ntaios G, Savopoulos C, Kiparoglou R, Agapakis D, Baltatzi M, Tsesmeli N, Hatzitolios A. Trend in incidence of cardiovascular risk factors in elderly and over-aged stroke patients between 2003 and 2007 in Greece. *Arch Gerontol Geriatr* 2010; **50**: e31-e35 [PMID: 19520441 DOI: 10.1016/j.archger.2009.05.002]

3 **Li W**, Prakash R, Chawla D, Du W, Didion SP, Filosa JA, Zhang Q, Brann DW, Lima VV, Tostes RC, Ergul A. Early effects of high-fat diet on neurovascular function and focal ischemic brain injury. *Am J Physiol Regul Integr Comp Physiol* 2013; **304**: R1001-R1008 [PMID: 23576615 DOI: 10.1152/ajpregu.00523.2012]

4 **Grundy SM**, Cleeman JI, Merz CN, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol* 2004; **24**: e149-e161 [PMID: 15297292 DOI: 161.10.1161/01.ATV.0000133317.49796.0E]

5 **Finch CE**, Tanzi RE. Genetics of aging. *Science* 1997; **278**: 407-411 [PMID: 9334291 DOI: 10.1126/science.278.5337.407]

6 **Holliday R**. Somatic mutations and ageing. *Mutat Res* 2000; **463**: 173-178 [PMID: 11018740 DOI: 10.1016/S1383-5742(00)00048-X]

7 **Carnes BA**, Olshansky SJ, Grahn D. Biological evidence for limits to the duration of life. *Biogerontology* 2003; **4**: 31-45 [PMID: 12652187 DOI: 10.1023/A: 1022425317536]

8 **Korpelainen H**. Fitness, reproduction and longevity among European aristocratic and rural Finnish families in the 1700s and 1800s. *Proc Biol Sci* 2000; **267**: 1765-1770 [PMID: 12233775 DOI: 10.1098/rspb.2000.1208]

9 **Gudmundsson H**, Gudbjartsson DF, Frigge M, Gulcher JR, Stefánsson K. Inheritance of human longevity in Iceland. *Eur J Hum Genet* 2000; **8**: 743-749 [PMID: 11039573 DOI: 10.1038/sj.ejhg.5200527]

10 **Wang DQ**. Aging per se is an independent risk factor for cholesterol gallstone formation in gallstone susceptible mice. *J Lipid Res* 2002; **43**: 1950-1959 [PMID: 12401894 DOI: 10.1194/jlr.M200078-JLR200]

11 **Segatto M**, Trapani L, Marino M, Pallottini V. Age- and sex-related differences in extra-hepatic low-density lipoprotein receptor. *J Cell Physiol* 2011; **226**: 2610-2616 [PMID: 21792919 DOI: 10.1002/jcp.22607]

12 **Trapani L**, Pallottini V. Age-Related Hypercholesterolemia and HMG-CoA Reductase Dysregulation: Sex Does Matter (A Gender Perspective). *Curr Gerontol Geriatr Res* 2010: 420139 [PMID: 20454643]

13 **Trapani L**, Segatto M, Incerpi S, Pallottini V. 3-Hydroxy-3-methylglutaryl coenzyme A reductase regulation by antioxidant compounds: new therapeutic tools for hypercholesterolemia? *Curr Mol Med* 2011; **11**: 790-797 [PMID: 21999146 DOI: 10.2174/156652411798062403]

14 **Marino M**, Pallottini V, D'Eramo C, Cavallini G, Bergamini E, Trentalance A. Age-related changes of cholesterol and dolichol biosynthesis in rat liver. *Mech Ageing Dev* 2002; **123**: 1183-1189 [PMID: 12044967 DOI: 10.1016/S0047-6374(02)00009-X]

15 **Pallottini V**, Martini C, Pascolini A, Cavallini G, Gori Z, Bergamini E, Incerpi S, Trentalance A. 3-Hydroxy-3-methylglutaryl coenzyme A reductase deregulation and age-related hypercholesterolemia: a new role for ROS. *Mech Ageing Dev* 2005; **126**: 845-851 [PMID: 15992608 DOI: 10.1016/j.mad.2005.02.009]

16 **Pallottini V**, Martini C, Cavallini G, Bergamini E, Mustard KJ, Hardie DG, Trentalance A. Age-related HMG-CoA reductase deregulation depends on ROS-induced p38 activation. *Mech Ageing Dev* 2007; **128**: 688-695 [PMID: 18031790 DOI: 10.1016/j.mad.2007.10.001]

17 **Trapani L**, Pallottini V. Hypercholesterolemia and 3-hydroxy 3-methylglutaryl Coenzyme A reductase regulation during ageing. *ScientificWorldJournal* 2009; **9**: 564-574 [PMID: 19578714 DOI: 10.1100/tsw.2009.81]

18 **Trapani L**, Violo F, Pallottini V. Hypercholesterolemia and 3-hydroxy-3-methylglutaryl coenzyme A reductase regulation in aged female rats. *Exp Gerontol* 2010; **45**: 119-128 [PMID: 19895880 DOI: 10.1016/j.exger.2009.10.014]

19 **Trapani L**, Segatto M, Ascenzi P, Pallottini V. Potential role of nonstatin cholesterol lowering agents. *IUBMB Life* 2011; **63**: 964-971 [PMID: 21990243 DOI: 10.1002/iub.522]

20 **Gotto AM**. Statin therapy and the elderly: SAGE advice? *Circulation* 2007; **115**: 681-683 [PMID: 17296867 DOI: 10.1161/CIRCULATIONAHA.106.678300]

21 **Istvan ES**, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001; **292**: 1160-1164 [PMID: 11349148 DOI: 10.1126/science.1059344]

22 **Rozman D**, Monostory K. Perspectives of the non-statin hypolipidemic agents. *Pharmacol Ther* 2010; **127**: 19-40 [PMID: 20420853 DOI: 10.1016/j.pharmthera.2010.03.007]

23 **Savopoulos CG**, Hatzitolios AI, Katsiki NA, Baltatzi M, Kosmidou M, Raikos N, Mikhailidis DP, Ziakas AG, Kaiafa G, Tsesmeli N. Sodium-lithium countertransport activity in healthy, dyslipidemic, and hypertensive individuals. *Angiology* 2008; **59**: 727-735 [PMID: 18840623 DOI: 10.1177/0003319708319784]

24 **Kosmidou MS**, Hatzitolios AI, Adamidou A, Giannopoulos S, Raikos N, Parharidis G, Milionis HJ. Effects of atorvastatin on red-blood cell Na(+)/Li(+) countertransport in hyperlipidemic patients with and without hypertension. *Am J Hypertens* 2008; **21**: 303-309 [PMID: 18202666 DOI: 10.1038/ajh.2007.61]

25 **Kosmidou M**, Hatzitolios AI, Molyva D, Raikos N, Savopoulos C, Daferera N, Kokkas V, Goulas A. An association study between catalase -262C& gt; T gene polymorphism, sodium-lithium countertransport activity, insulin resistance, blood lipid parameters and their response to atorvastatin, in Greek dyslipidaemic patients and normolipidaemic controls. *Free Radic Res* 2009; **43**: 385-389 [PMID: 19274593 DOI: 10.1080/10715760902783293]

26 **Callegari S**, Gregory PA, Sykes MJ, Bellon J, Andrews S, McKinnon RA, de Barros Lopes MA. Polymorphisms in the mitochondrial ribosome recycling factor EF-G2mt/MEF2 compromise cell respiratory function and increase atorvastatin toxicity. *PLoS Genet* 2012; **8**: e1002755 [PMID: 22719265 DOI: 10.1371/journal.pgen.1002755]

27 **Elens L**, Becker ML, Haufroid V, Hofman A, Visser LE, Uitterlinden AG, Stricker BCh, van Schaik RH. Novel CYP3A4 intron 6 single nucleotide polymorphism is associated with simvastatin-mediated cholesterol reduction in the Rotterdam Study. *Pharmacogenet Genomics* 2011; **21**: 861-866 [PMID: 21946898 DOI: 10.1097/FPC.0b013e32834c6edb]

28 **Hutz MH**, Fiegenbaum M. Impact of genetic polymorphisms on the efficacy of HMG-CoA reductase inhibitors. *Am J Cardiovasc Drugs* 2008; **8**: 161-170 [PMID: 18533737 DOI: 10.2165/00129784-200808030-00003]

29 **Cham S**, Evans MA, Denenberg JO, Golomb BA. Statin-associated muscle-related adverse effects: a case series of 354 patients. *Pharmacotherapy* 2010; **30**: 541-553 [PMID: 20500044 DOI: 10.1592/phco.30.6.541]

30 **Trapani L**, Melli L, Segatto M, Trezza V, Campolongo P, Jozwiak A, Swiezewska E, Pucillo LP, Moreno S, Fanelli F, Linari M, Pallottini V. Effects of myosin heavy chain (MHC) plasticity induced by HMGCoA-reductase inhibition on skeletal muscle functions. *FASEB J* 2011; **25**: 4037-4047 [PMID: 21798954 DOI: 10.1096/fj.11-184218]

31 **Martini C**, Pallottini V, De Marinis E, Marino M, Cavallini G, Donati A, Straniero S, Trentalance A. Omega-3 as well as caloric restriction prevent the age-related modifications of cholesterol metabolism. *Mech Ageing Dev* 2008; **129**: 722-727 [PMID: 18930075 DOI: 10.1016/j.mad.2008.09.010]

32 **Sevov M**, Elfineh L, Cavelier LB. Resveratrol regulates the expression of LXR-alpha in human macrophages. *Biochem Biophys Res Commun* 2006; **348**: 1047-1054 [PMID: 16901463 DOI: 10.1016/j.bbrc.2006.07.155]

33 **Cho IJ**, Ahn JY, Kim S, Choi MS, Ha TY. Resveratrol attenuates the expression of HMG-CoA reductase mRNA in hamsters. *Biochem Biophys Res Commun* 2008; **367**: 190-194 [PMID: 18166149 DOI: 10.1016/j.bbrc.2007.12.140]

34 **Sesso HD**, Gaziano JM, Liu S, Buring JE. Flavonoid intake and the risk of cardiovascular disease in women. *Am J Clin Nutr* 2003; **77**: 1400-1408 [PMID: 12791616]

35 **Punithavathi VR**, Prince PS. Combined effects of quercetin and alpha-tocopherol on lipids and glycoprotein components in isoproterenol induced myocardial infarcted Wistar rats. *Chem Biol Interact* 2009; **181**: 322-327 [PMID: 19595682 DOI: 10.1016/j.cbi.2009.07.002]

36 **Brown GR**, Hollinshead DM, Stokes ES, Clarke DS, Eakin MA, Foubister AJ, Glossop SC, Griffiths D, Johnson MC, McTaggart F, Mirrlees DJ, Smith GJ, Wood R. Quinuclidine inhibitors of 2,3-oxidosqualene cyclase-lanosterol synthase: optimization from lipid profiles. *J Med Chem* 1999; **42**: 1306-1311 [PMID: 10197973 DOI: 10.1021/jm990038q]

37 **Lee SH**, Park YB, Bae KH, Bok SH, Kwon YK, Lee ES, Choi MS. Cholesterol-lowering activity of naringenin via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and acyl coenzyme A: cholesterol acyltransferase in rats. *Ann Nutr Metab* 1999; **43**: 173-180 [PMID: 10545673 DOI: 10.1159/000012783]

38 **Song BL**, DeBose-Boyd RA. Insig-dependent ubiquitination and degradation of 3-hydroxy-3-methylglutaryl coenzyme a reductase stimulated by delta- and gamma-tocotrienols. *J Biol Chem* 2006; **281**: 25054-25061 [PMID: 16831864 DOI: 10.1074/jbc.M605575200]

39 **Qureshi AA**, Burger WC, Peterson DM, Elson CE. The structure of an inhibitor of cholesterol biosynthesis isolated from barley. *J Biol Chem* 1986; **261**: 10544-10550 [PMID: 3733719]

40 **Borges F**, Roleira F, Milhazes N, Santana L, Uriarte E. Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. *Curr Med Chem* 2005; **12**: 887-916 [PMID: 15853704 DOI: 10.2174/0929867053507315]

41 **Pedersen JZ**, Oliveira C, Incerpi S, Kumar V, Fiore AM, De Vito P, Prasad AK, Malhotra SV, Parmar VS, Saso L. Antioxidant activity of 4-methylcoumarins. *J Pharm Pharmacol* 2007; **59**: 1721-1728 [PMID: 18053335 DOI: 10.1211/jpp.59.12.0015]

42 **Trapani L**, Segatto M, Simeoni V, Balducci V, Dhawan A, Parmar VS, Prasad AK, Saso L, Incerpi S, Pallottini V. Short- and long-term regulation of 3-hydroxy 3-methylglutaryl coenzyme A reductase by a 4-methylcoumarin. *Biochimie* 2011; **93**: 1165-1171 [PMID: 21530605 DOI: 10.1016/j.biochi.2011.04.009]

43 **da Rocha JT**, Pinton S, Mazzanti A, Mazzanti CM, Beckemann DV, Nogueira CW, Zeni G. Diphenyl diselenide ameliorates cognitive deficits induced by a model of menopause in rats. *Behav Pharmacol* 2012; **23**: 98-104 [PMID: 22139607 DOI: 10.1097/FBP.0b013e32834ed849]

44 **da Rocha JT**, Sampaio TB, Santos Neto JS, Nogueira CW, Zeni G. Cognitive effects of diphenyl diselenide and estradiol treatments in ovariectomized mice. *Neurobiol Learn Mem* 2013; **99**: 17-24 [PMID: 23085182 DOI: 10.1016/j.nlm.2012.10.005]

45 **de Bem AF**, Farina M, Portella Rde L, Nogueira CW, Dinis TC, Laranjinha JA, Almeida LM, Rocha JB. Diphenyl diselenide, a simple glutathione peroxidase mimetic, inhibits human LDL oxidation in vitro. *Atherosclerosis* 2008; **201**: 92-100 [PMID: 18440006 DOI: 10.1016/j.atherosclerosis.2008.02.030]

46 **da Rocha JT**, Sperança A, Nogueira CW, Zeni G. Hypolipidaemic activity of orally administered diphenyl diselenide in Triton WR-1339-induced hyperlipidaemia in mice. *J Pharm Pharmacol* 2009; **61**: 1673-1679 [PMID: 19958591]

47 **Hort MA**, Straliotto MR, Netto PM, da Rocha JB, de Bem AF, Ribeiro-do-Valle RM. Diphenyl diselenide effectively reduces atherosclerotic lesions in LDLr -/- mice by attenuation of oxidative stress and inflammation. *J Cardiovasc Pharmacol* 2011; **58**: 91-101 [PMID: 21558882]

48 **Altmann SW**, Davis HR, Zhu LJ, Yao X, Hoos LM, Tetzloff G, Iyer SP, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science* 2004; **303**: 1201-1204 [PMID: 14976318 DOI: 10.1126/science.1093131]

49 **Ge L**, Wang J, Qi W, Miao HH, Cao J, Qu YX, Li BL, Song BL. The cholesterol absorption inhibitor ezetimibe acts by blocking the sterol-induced internalization of NPC1L1. *Cell Metab* 2008; **7**: 508-519 [PMID: 18522832 DOI: 10.1016/j.cmet.2008.04.001]

50 **Pandor A**, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A, Durrington PN, Chilcott J. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 2009; **265**: 568-580 [PMID: 19141093]

51 **Sallam A**, Kashani S, Sherafat H. Healon5 and corneal wound burn during phacoemulsification. *J Cataract Refract Surg* 2007; **33**: 754; author reply 754-755 [PMID: 17466828]

52 **Thomas JE**, Tershakovec AM, Jones-Burton C, Sayeed RA, Foody JM. Lipid lowering for secondary prevention of cardiovascular disease in older adults. *Drugs Aging* 2010; **27**: 959-972 [PMID: 21087066 DOI: 10.2165/11539550-000000000-00000]

53 **Hatzitolios A**, Savopoulos C, Lazaraki G, Sidiropoulos I, Haritanti P, Lefkopoulos A, Karagiannopoulou G, Tzioufa V, Dimitrios K. Efficacy of omega-3 fatty acids, atorvastatin and orlistat in non-alcoholic fatty liver disease with dyslipidemia. *Indian J Gastroenterol* 2004; **23**: 131-134 [PMID: 15333967]

54 **Han TS**, Tajar A, Lean ME. Obesity and weight management in the elderly. *Br Med Bull* 2011; **97**: 169-196 [PMID: 21325341 DOI: 10.1093/bmb/ldr002]

55 **Sakai T**, Kamanna VS, Kashyap ML. Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. *Arterioscler Thromb Vasc Biol* 2001; **21**: 1783-1789 [PMID: 11701466 DOI: 10.1161/hq1001.096624]

56 **Vosper H**. Niacin: a re-emerging pharmaceutical for the treatment of dyslipidaemia. *Br J Pharmacol* 2009; **158**: 429-441 [PMID: 19627285 DOI: 10.1111/j.1476-5381.2009.00349.x]

57 [**Kühnast S**](http://www.ncbi.nlm.nih.gov/pubmed?term=K%C3%BChnast%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23840481)**,** [Louwe MC](http://www.ncbi.nlm.nih.gov/pubmed?term=Louwe%20MC%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [Heemskerk MM](http://www.ncbi.nlm.nih.gov/pubmed?term=Heemskerk%20MM%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [Pieterman EJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Pieterman%20EJ%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [van Klinken JB](http://www.ncbi.nlm.nih.gov/pubmed?term=van%20Klinken%20JB%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [van den Berg SA](http://www.ncbi.nlm.nih.gov/pubmed?term=van%20den%20Berg%20SA%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [Smit JW](http://www.ncbi.nlm.nih.gov/pubmed?term=Smit%20JW%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [Havekes LM](http://www.ncbi.nlm.nih.gov/pubmed?term=Havekes%20LM%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [Rensen PC](http://www.ncbi.nlm.nih.gov/pubmed?term=Rensen%20PC%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [van der Hoorn JW](http://www.ncbi.nlm.nih.gov/pubmed?term=van%20der%20Hoorn%20JW%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [Princen HM](http://www.ncbi.nlm.nih.gov/pubmed?term=Princen%20HM%5BAuthor%5D&cauthor=true&cauthor_uid=23840481), [Jukema JW](http://www.ncbi.nlm.nih.gov/pubmed?term=Jukema%20JW%5BAuthor%5D&cauthor=true&cauthor_uid=23840481). Niacin Reduces Atherosclerosis Development in APOE\*3Leiden.CETP Mice Mainly by Reducing NonHDL-Cholesterol. *PLoS One* 2013; **8**: e66467 [PMID: 23840481 DOI: 10.1371/journal.pone.0066467]

58**Tenenbaum A**, Fisman EZ. Fibrates are an essential part of modern anti-dyslipidemic arsenal: spotlight on atherogenic dyslipidemia and residual risk reduction. *Cardiovasc Diabetol* 2012; **11**: 125 [PMID: 23057687]

59**avidson MH**. Novel nonstatin strategies to lower low-density lipoprotein cholesterol. *Curr Atheroscler Rep* 2009; **11**: 67-70 [PMID: 19080731 DOI: 10.1007/s11883-009-0011-0]

60 **Meade T**, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002; **325**: 1139 [PMID: 12433762 DOI: 10.1136/bmj.325.7373.1139]

61 **Merki E**, Graham MJ, Mullick AE, Miller ER, Crooke RM, Pitas RE, Witztum JL, Tsimikas S. Antisense oligonucleotide directed to human apolipoprotein B-100 reduces lipoprotein(a) levels and oxidized phospholipids on human apolipoprotein B-100 particles in lipoprotein(a) transgenic mice. *Circulation* 2008; **118**: 743-753 [PMID: 18663084 DOI: 10.1161/CIRCULATIONAHA.108.786822]

62 **Bays HE**, Neff D, Tomassini JE, Tershakovec AM. Ezetimibe: cholesterol lowering and beyond. *Expert Rev Cardiovasc Ther* 2008; **6**: 447-470 [PMID: 18402536 DOI: 10.1586/14779072.6.4.447]

63 **Huang LZ**, Zhu HB. Novel LDL-oriented pharmacotherapeutical strategies. *Pharmacol Res* 2012; **65**: 402-410 [PMID: 22306845 DOI: 10.1016/j.phrs.2012.01.007]

64 **Peterson AS,** Fong LG, Young SG. PCSK9 function and physiology. *J Lipid Res*

2008; **49:** 1595-1599

65 **Seidah NG**, Prat A. The biology and therapeutic targeting of the proprotein convertases. *Nat Rev Drug Discov* 2012; **11**: 367-383 [PMID: 22679642 DOI: 10.1038/nrd3699]

66 **Graham MJ**, Lemonidis KM, Whipple CP, Subramaniam A, Monia BP, Crooke ST, Crooke RM. Antisense inhibition of proprotein convertase subtilisin/kexin type 9 reduces serum LDL in hyperlipidemic mice. *J Lipid Res* 2007; **48**: 763-767 [PMID: 17242417 DOI: 10.1194/jlr.C600025-JLR200]

67 **Gupta N**, Fisker N, Asselin MC, Lindholm M, Rosenbohm C, Ørum H, Elmén J, Seidah NG, Straarup EM. A locked nucleic acid antisense oligonucleotide (LNA) silences PCSK9 and enhances LDLR expression in vitro and in vivo. *PLoS One* 2010; **5**: e10682 [PMID: 20498851 DOI: 10.1371/journal.pone.0010682]

68 **Shan L**, Pang L, Zhang R, Murgolo NJ, Lan H, Hedrick JA. PCSK9 binds to multiple receptors and can be functionally inhibited by an EGF-A peptide. *Biochem Biophys Res Commun* 2008; **375**: 69-73 [PMID: 18675252 DOI: 10.1016/j.bbrc.2008.07.106]

69 **Duff CJ**, Scott MJ, Kirby IT, Hutchinson SE, Martin SL, Hooper NM. Antibody-mediated disruption of the interaction between PCSK9 and the low-density lipoprotein receptor. *Biochem J* 2009; **419**: 577-584 [PMID: 19196236 DOI: 10.1042/BJ20082407]

70 **Lambert G**, Sjouke B, Choque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. *J Lipid Res* 2012; **53**: 2515-2524 [PMID: 22811413 DOI: 10.1194/jlr.R026658]

71 **Petrides F**, Shearston K, Chatelais M, Guilbaud F, Meilhac O, Lambert G. The promises of PCSK9 inhibition. *Curr Opin Lipidol* 2013; **24**: 307-312 [PMID: 23817198 DOI: 10.1097/MOL.0b013e328361f62d]

72 **Chen XW**, Wang H, Bajaj K, Zhang P, Meng ZX, Ma D, Bai Y, Liu HH, Adams E, Baines A, Yu G, Sartor MA, Zhang B, Yi Z, Lin J, Young SG, Schekman R, Ginsburg D. SEC24A deficiency lowers plasma cholesterol through reduced PCSK9 secretion. *Elife* 2013; **2**: e00444 [PMID: 23580231]

73 **Lee SN**, Prodhomme E, Lindberg I. Prohormone convertase 1 (PC1) processing and sorting: effect of PC1 propeptide and proSAAS. *J Endocrinol* 2004; **182**: 353-364 [PMID: 15283695 DOI: 10.1677/joe.0.1820353]

74 **Marazzi G**, Cacciotti L, Pelliccia F, Iaia L, Volterrani M, Caminiti G, Sposato B, Massaro R, Grieco F, Rosano G. Long-term effects of nutraceuticals (berberine, red yeast rice, policosanol) in elderly hypercholesterolemic patients. *Adv Ther* 2011; **28**: 1105-1113 [PMID: 22113535 DOI: 10.1007/s12325-011-0082-5]

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**Table 1 Percentage of studies performed on hypocholesterolemic drugs and elderly**

|  |  |  |  |
| --- | --- | --- | --- |
| Drugs | Number of PubMed papers key word | |  |
|  | hypercholesterolemia | hypercholesterolemia and ageing |  |
| Statins | 5980 | 89 | 14% |
| Omega3 fatty acids | 246 | 14 | 6% |
| Resveratrol | 35 | 2 | 6% |
| Flavonoids | 229 | 6 | 3% |
| Coumarins | 40 | 0 | 0% |
| Organioselenium compounds | 4 | 0 | 0% |
| Ezetimibe | 658 | 6 | 1% |
| Niacin | 397 | 8 | 2% |
| Fibrates | 860 | 9 | 1% |
| Bile acid sequestrants | 117 | 0 | 0% |
| PCSK9 | 283 | 2 | 1% |