

Review

# Development of Dyslipidemia in Atherosclerosis and Modern Approaches to its Treatment

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## Abstract

Dyslipidemia is one of the key features in the pathogenesis of atherosclerosis, however, many points in the progression of this pathological phenomenon remain unclear. In this review, we will consider the significance of various lipoproteins in the progression of atherosclerosis, the general pattern of dyslipidemia development and its role in the pathogenesis of atherosclerosis, as well as new approaches to the treatment of dyslipidemia, which will potentially reduce the disadvantages of existing therapies and increase drug efficacy.

## Keywords

atherosclerosis; dyslipidemia; lipoproteins

## Introduction

Atherosclerosis is the result of hyperlipidemia and lipid oxidation and has always been the leading cause of death in developed countries. It is a disease of the vascular intima, which may involve the entire vascular system from the aorta to the coronary arteries, and is characterized by intimal plaques [1]. It is primarily a lipid-dependent process initiated by the accumulation of low-density lipoproteins and residual lipoprotein particles, as well as an active inflammatory process in the focal areas of the arteries, especially in areas of impaired non-laminar blood flow at the arterial bifurcation points, and is considered the main cause of atherosclerotic cardiovascular disease (ASCVD), leading to heart attacks, stroke, and peripheral arterial disease. Atherosclerosis can manifest as coronary heart disease (CHD), cerebrovascular disease (CVD), transient ischemic attack (TIA), peripheral arterial disease (PAD), abdominal aneurysms, and renal artery stenosis in men [2].

The exact causes and risk factors for atherosclerosis are unknown; however, certain conditions or habits can

make you more likely to develop the condition. Most risk factors include high cholesterol and low-density lipoprotein levels, low blood levels of high-density lipoprotein, hypertension, smoking, diabetes mellitus, obesity, sedentary lifestyle, and age [3].

Since atherosclerosis is predominantly an asymptomatic disease, it is difficult to accurately determine the incidence. Atherosclerosis is considered the main cause of cardiovascular disease. Atherosclerotic cardiovascular diseases mainly affect the heart and brain: coronary heart disease (CHD) and ischemic stroke. Ischemic heart disease (IHD) and stroke are the first and fifth causes of death in the world, respectively [4].

Atherosclerosis mainly develops as a result of a continuous process of damage to the arterial wall due to the retention of lipids by entrapment of the intima by a matrix such as proteoglycans, which leads to modification, which in turn exacerbates chronic inflammation in vulnerable areas of the arteries and plays an important role in all phases of progression of atherogenesis. This process begins with nascent fatty streaks in the intima of the arteries, which develop into fibrous plaques and develop into complex atherosclerotic lesions prone to rupture. In addition, stenosis due to inward expansion of atheroma can lead to occlusion of vessels, such as coronary ones. However, symptomatic disease can be mitigated by abundant collateral circulation [5].

Treatment of atherosclerosis is based on the control of lipoprotein levels. However, first of all, it is necessary to change the patient's lifestyle, namely dietary nutrition, physical activity and smoking cessation. If this proves insufficient, then drug therapy should be included in lifestyle optimization. The main drug for lowering cholesterol and reducing cardiovascular events are statins. Statins are generally very effective drugs that have shown a consistent reduction in clinical events with a very good safety profile in the vast majority of well-conducted trials. However, important side effects may occur, making the compound sometimes unsuitable for some individual patients [6]. Other drugs such as cholesterol absorption inhibitors, bile acid sequestrants, proprotein convertase inhibitors subtilisin/kexin

**Table 1. Characteristics of lipoprotein groups.**

Group of lipoproteins	Role in lipid metabolism	Role in atherosclerosis
Chylomicrons and remnants of chylomicrons	Delivery of dietary cholesterol and triglycerides to peripheral tissues and the liver [8].	Plaque cholesterol formation [8].
Very low density lipoproteins and intermediate density lipoproteins	Absorption of triglycerides by cardiomyocytes, skeletal muscle, and adipose tissue [9,10].	Triggerring of a cascade of atherosclerotic lipid, immunological, and inflammatory processes [9].
Low density lipoproteins	Transport of cholesterol to peripheral tissues [11].	Endothelial injury, macrophage chemoattraction, and arterial pathology [11]. Plaque cholesterol formation [8].
High density lipoproteins	Transport of cholesterol from peripheral tissues to the liver [12–14].	Antioxidant and anti-inflammatory functions that can inhibit atherosclerosis [12].
Lipoprotein A	As LDL	The formation of foam cells [8]. Lp (a) impairs fibrinolysis and enhances coagulation [8].

LDL, low density lipoproteins; Lp (a), Lipoprotein a.

type 9 (PCSK9) are also used to treat atherosclerosis. However, the relatively high cost of the compounds and the lack of significant results in large randomized controlled trials (RCTs) still limit their use in clinical practice [7].

Existing methods of atherosclerosis treatment have a large number of disadvantages and side effects. Thus, there is an urgent need to develop new, convenient and effective approaches to the treatment of the disease.

## Normal Lipid Metabolism

All lipoproteins can be divided into these groups: chylomicrons and remnants of chylomicrons, very low density lipoproteins (VLDL) and intermediate density lipoproteins, low density lipoproteins (LDL), high density lipoproteins (HDL) and lipoprotein A (Lp (a)). All of them are very important for processes connected with the lipid metabolism and their ratio determines the risk of developing various metabolic disorders, including dyslipidemia. Information about these groups of lipoproteins is presented in Table 1 (Ref. [8–14]).

Three phases constitute lipid metabolism: reverse cholesterol transport, endogenous and exogenous routes. Lipids are transported from intestine to liver and other organs in exogenous pathway. Bile salts, phospholipids, free cholesterol, free fatty acids (FFA), and monoglycerides combine into mixed micelles in the small intestine, ensuring that the intestinal mucosa absorbs them [15]. The Niemann-Pick C1-Like 1 (NPC1L1) transporter, which is found in the apical membrane of hepatocytes and at the edge of the jejunal enterocyte membrane, mediates the absorption of stanols, plant sterols, and cholesterol. Like all cells, enterocytes contain an extrusion mechanism that incorporates G5 and G8, as well as many proteins from the ATP-binding cassette transporter 1 (ABCA1) superfamily. The process of reabsorbing sterols and returning them to the intestinal lumen is carried out by the heterodimer

membrane transporters ATP-binding cassette sub-family G member 5 (ABCG5) and ATP Binding Cassette Subfamily G Member 8 (ABCG8). Half of the cholesterol that enterocytes take and do not revert back to the gut lumen via the ABCG5/8 process disperses into the endoplasmic reticulum, where the enzyme acetylcholesterol acyltransferase-2 (ACAT2) reesterifies it [16]. A protein known as microsomal triglyceride transfer protein (MTP) combines esterified cholesterol with other molecules to generate the first lipoproteins known as chylomicrons, which are responsible for delivering absorbed lipids into the body. XM are carried to the lymphatic system, where they reach the systemic circulation via the thoracic duct. They eventually pick up Apo E and Apo C-II, which are carried by HDL, in the circulation. Under typical circumstances and with an empty stomach, they circulate for a maximum of 12 hours. XM is changed into a smaller particle known as the chylomicron residue by the enzyme lipoprotein lipase. This particle is distinguished by the presence of Apo E. Adipocytes and muscle cells absorb the FFAs. Fatty acids (FA) in the liver might come from internal or dietary sources. The intestinal lumen emulsifies dietary triglycerides (TG) once they are hydrolyzed, mostly by pancreatic lipase, producing free FA and sn-2-monoacylglycerols as byproducts [17]. These lipid molecules are taken up by enterocytes and resynthesized into TG after emulsification. Chylomicrons are formed from TG, which are then released into the lymphatic system and eventually end up in the plasma [17]. Muscle and adipose tissue absorb a significant amount of chylomicron TG because lipoprotein lipase, which is expressed on the luminal surfaces of capillary endothelial cells in these tissues, is active. When the chylomicron remnants are ingested by receptor-mediated endocytosis, FA are released and the remaining TG is transported to the liver [17]. As a result, the pace at which dietary fat is eliminated from the bloodstream is determined by LPL activity, which is tightly controlled throughout the bloodstream [18].

The creation of VLDL, which is generated by the liver's endoplasmic reticulum and carries triglycerides and apolipoproteins, is the first step in endogenous lipid metabolism. The Golgi apparatus secretes immature VLDL into and then in the circulation, and then in the plasma, fully formed VLDL absorb more Apo C-II and Apo E from HDL. The enzymatic cholesterol ester transfer protein (CETP) mediates the transfer of cholesterol from VLDL to cholesterol acceptors [19]. The LPL enzyme uses the triglyceride materials of VLDL as a suitable substrate to hydrolyze lipoproteins and unleash free fatty acids (FFA), which can be stored in adipocytes or used as muscle fuel. VLDL residues are smaller VLDL molecules as a result of hydrolysis. Lipids and apolipoproteins are also freed and absorbed into the HDL fraction during the degradation of chylomicrons (HM). Apo B100 and E make up their makeup of apolipoproteins. Hepatic lipase (PL) mediates a complicated process that converts the other half of the LDL particles to LDL. It is assumed that B/E receptors take up about half of the LDL particles in the liver, where they are absorbed and hydrolysed in hepatocytes. PL is engaged in HDL metabolism and regulates LDL triglyceride lipolysis. LDL catabolism produces low-density lipoproteins [20]. LDL is responsible for delivering and transporting cholesterol to all cells, including the liver and peripheral organs. Aspartate transaminase (ASAT)-1, acyl coenzyme A cholesterol acyltransferase, 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMG-CoA reductase), and the production of several LDL receptors are all inhibited by released cholesterol, which also increases acyl coenzyme A cholesterol acyltransferase [21].

HDL cholesterol is transported from peripheral tissues to the liver by reverse transport of cholesterol. There, it undergoes processing and is either used to generate bile acids or eliminated as bile to the intestines. Approximately half of the intestinal sterols and 95% of the bile acids are reverted to the liver for processing through the enterohepatic cycle, which is where cholesterol and bile acids enter [16].

## Model of Atherosclerosis Progression Involving Lipoproteins

### *Endothelial Changes and Regional Distribution of Plaques*

A variety of pathophysiological processes underlying atherosclerosis and the normal distribution of atherosclerotic lesions are explained by the alterations that endothelial cells experience, both connected to and unrelated to lipoproteins [22,23]. Endothelial cell failure leads the way in accessing the intimal extracellular matrix, while LDL and other tiny and atherogenic lipoproteins undergo structural and oxidative alterations that ultimately result in artery intima entrapment that attracts macrophages and other cells

of the immune system [24,25]. Nitric oxide (NO), a powerful regulator of vascular function and an inhibitor of vascular smooth muscle cell (SMC) proliferation, is hampered by oxidative damage to the endothelium. NO also plays a significant role in inhibiting LDL oxidation and leukocyte extravasation from the circulation into the artery intima [26]. Endothelin-1 (ET1), which interacts with NO in the control of arterial tone, signals changes in endothelial production of adhesion molecules, and draws significant inflammatory cells like macrophages while controlling extracellular matrix enzymes that enhance intimal alterations, are additional chemical mediators of endothelial dysfunction [27].

Not varying NO and other chemical signal levels, but rather a regional reorganization of endothelium phenotypes in response to local hemodynamic factors, are the endothelial alterations that shed the most light on the regional pathophysiology of atherosclerosis. Atherosclerosis plaques often develop near the arterial circulation's points of curvature and bifurcation, where characteristic patterns of elevated shear stress are noted [28]. Especially in contrast to endothelial cells in more hemodynamically favorable arterial beds, which have an ellipsoidal shape, coaxial alignment, and an endothelial glycocalyx that protects against lipoprotein extravasation, endothelial cells in areas of higher shear stress have a cuboidal morphology, increased cell turnover, and reduced endothelial barrier function, all of which combined enhance migration of lipoproteins and inflammatory cells [29]. Critical endothelial alterations that further worsen the migration of lipoproteins, leukocytes, smooth muscle cells (SMCs), and fibroblasts are crucial for plaque development and the clinical implications of plaque enlargement and rupture [30]. While lipoproteins, especially LDL and apo B-100, have large sizes, oxidative profiles, and atherogenic risks, they are not the only factors contributing to atherosclerosis.

### *Atherosclerotic Plaque Initiation: Foam Cell Formation*

Circulating LDL and, to a lesser extent, VLDL and LDL migrate from the plasma and persist in the extracellular matrix of the intima of the membrane as a result of ongoing endothelium destruction in artery curvature and bifurcation regions [31,32]. Subendothelial buildup of LDL and VLDL residues quickens the endothelial initiation of the NF- $\kappa$ B pathway, which in turn boosts the production of pro-inflammatory receptors, cytokines that encourage monocyte migration, and sticky proteins like vascular cell adhesion molecule 1 (VCAM-1) and P-selectin on the endothelium [33]. Apo B-100 is oxidized to produce ox-LDL, a powerful macrophage scavenger receptor ligand, to a greater amount in LDL as LDL, VLDL, VLDL, LDL, and Lp(a) residues build up in the artery's intima. The folding, activation, and transendothelial migration of monocytes, wherein they differentiate from monocytes to macrophages, are mediated by endothelial activation and overexpression

of adhesion molecules [34]. In contrast to cholesterol ingested by macrophages through the LDL receptor, stored ox-LDL does not negatively feedback scavenger receptor expression, sustaining continuous oxidation and absorption of cholesterol that results in the capture of newly generated foam cells in the intima of arteries owing to reduced mobility [35]. Stored ox-LDL binds with two macrophage receptors, scavenger receptors classes A and B.

VLDL and Lp (a) are crucial for endothelial activation, even though LDL predominates in the cycle of endothelial injury, assimilation by macrophages, foam cell production, and inflammatory transduction [9]. Oxidized VLDL promotes the production of plasminogen activator inhibitor 1 (PAI-1), a protein that decreases the transformation of plasminogen to plasmin and hence plasmin-mediated deconstruction of cholesterol clumps. Endothelial cells exposed to VLDL triglycerides also boost the development of selectins and other proteins that enable monocyte entrance into the artery intima [36]. Lp (a) interacts with certain macrophage surface integrin proteins to facilitate monocyte extravasation. Following absorption by macrophages, these interactions upregulate the production of tumor necrosis factor (TNF), interleukin-1 (IL-1), and monocyte chemoattractant protein (MCP-1), which draws in more macrophages and increases the quantity of foam cells [37].

#### *Plaque Development: Inflammatory Cells and Smooth Muscle Cells Participation*

Apart from being absorbed by macrophages, ox-LDL functions as a chemokine that triggers several immune pathways, resulting in the migration and stimulation of extra monocytes and other cells of the immune system [38]. Through a complex interaction between the innate and adaptive immune systems, foam cells and apoptotic cell debris are removed from dendritic cells and T cells when leukocytes adhere and extravasate, despite the fact that retention of LDL, VLDL, LDL, and Lp (a) residues leads to the formation of foam cells as an critical initial step in plaque development [39]. When antigens are presented to T cells by atherosclerotic lesion macrophages which develop into M1 inflammatory macrophages, T cells get activated and produce pro-inflammatory cytokines including IL-1 and IL-6. This causes local inflammation of the lesion, additional foam cell production, necrosis, and death [40].

Like macrophages, foam cells are phagocytosed by dendritic cells; during this process, antigen presentation to T cells triggers the production of a cytokine that is pro-inflammatory; further phagocytosis impairs dendritic cell motility, which results in the development of dendritic foam cells [41].

The inflammatory pathways, lipid buildup, and endothelial dysfunction all combine to cause profound alterations in SMC physiology. The most significant factor de-

termining the stability or susceptibility of atherosclerotic plaques is the activation, migration, and phenotypic changing of SMCs in the native arterial environment [42]. External vascular remodeling results from the migration and proliferation of SMCs, which boost the synthesis of extracellular matrix elements like elastin and proteoglycans in an effort to correct the internal architectural deformities brought on by the buildup of subendothelial lipoproteins. The creation of SMC collagen plays a crucial role in the establishment of the fibrous cap in atherosclerotic plaques. The release of transforming growth factor beta (TGF- $\beta$ ) from the plaque signals the proliferation of SMC [43].

## **New Approaches in the Treatment of Dyslipidemia**

### *Nanoparticles Containing Statins*

The use of statins is the accepted standard of care for dyslipidemia, and these compounds are used as first-line therapy to reduce cardiovascular risk. The mechanism of action of statins is based on the competitive inhibition of HMG-CoA reductase, an enzyme involved in the process of cholesterol synthesis [44]. In addition to lowering cholesterol levels, statins also play a role in improving endothelial function, have antithrombotic and anti-inflammatory effects on vascular endothelium, which characterizes them as a highly effective agent in the treatment of atherosclerosis [45]. However, despite the multiple efficacy of statins shown in the treatment of atherosclerosis, they are characterized by low bioavailability [46]. As a result, treatment over a long period (especially with the use of high doses of these drugs) carries a high risk of developing severe side effects, including myopathy, hemorrhagic stroke and neurological disorders [45]. In addition, it is noted that long-term statin therapy is the cause of a decrease in coenzyme Q up to 40%, the lack of which also leads to serious consequences [47]. It is also known that there are patients for whom statins are contraindicated at any dose [46]. To improve bioavailability, reduce the likelihood of side effects, and increase therapeutic efficacy, several variants of nanoparticles that are carriers of statins have been developed: polymeric nanoparticles, nanoparticles based on chitosan, lipid nanoparticles, nanoparticles based on cerium oxide, and other options for which studies have been conducted on animals, the results of which were comparable to traditional methods of statin delivery, and often were better (more details in Table 2, Ref. [46,48–60]).

### *New Variants of PCSK9 Inhibition*

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secretory protease that is released into plasma by hepatocytes and causes degradation of LDL receptors, result-

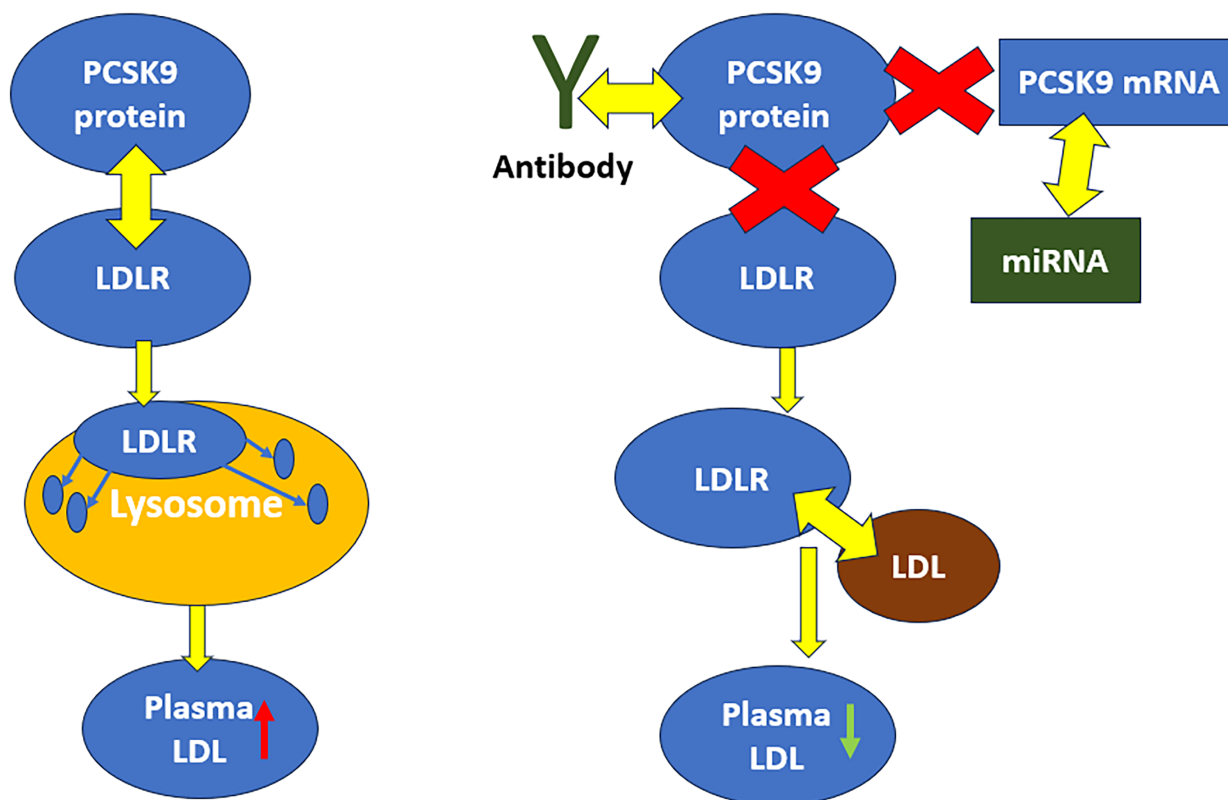
**Table 2. Results of animal studies on the use of nanoparticles as statin carriers.**

Type of nanoparticles	Distinctive features of nanoparticles	Results of the use of nanoparticles
Polymer nanoparticles	Nanoparticles from lactic glycolic acid, polycaprolactone and cellulose [46].	Increased bioavailability of statins, in particular by 66% [48] and 3.5 times [49]. No or minor side effects [46]. Reduced inflammation as a result of reduced iNOS activity [50] and lipid peroxidation in the liver, as well as the levels of IL 1 and IL 6 [51]. Decreased thrombotic potential [52].
Chitosan nanoparticles	Chitosan increases the stability of liposomes [53]. It alone can lower cholesterol levels [54].	Improved bioavailability [55]. Better efficacy in reducing dyslipidemia in comparison with a single administration of the drug [55].
Cerium oxide nanoparticles	Cerium oxide nanoparticles have the ability to eliminate ROS [56].	Higher antioxidant, anti-inflammatory and anti-apoptotic activity in compared with a single administration of the drug [56].
Lipid nanoparticles	Nanoparticles of 2 types: solid lipid nanoparticles (SLN) and nanostructured lipid carrier (NLC) [57].	Better bioavailability and absorption of drugs in comparison with the introduction of free statins [58]. Possibility of delivery directly to atherosclerotic plaques [59]. Better results in lowering total cholesterol, LDL, triglycerides and increasing HDL levels compared with the administration of free statins [60]. Inhibition of inflammation and reduction of atherosclerotic plaques without the development of hepatotoxicity [59].

ROS, reactive oxygen species; IL 1, interleikin 1; HDL, high-density lipoprotein.

ing in blocking of LDL uptake from plasma [61]. Given these features of this protein, PCSK9 has become a promising target in the treatment of dyslipidemia. The general mechanism of action of PCSK9 inhibitors is based on the inhibition of PCSK9 binding to LDL receptors, which prevents the destruction of these receptors. Initially released into clinical practice, PCSK9 inhibitors were monoclonal antibodies to this protein. Thus, the monoclonal antibodies alirocumab and evolocumab, approved for clinical use in 2015, in addition to the ability to reduce LDL concentration, also changed the lipid profile, increasing HDL levels and reducing total cholesterol, which ultimately led to a decrease in the volume of atherosclerotic plaques [46]. It is believed that the use of monoclonal antibodies to PCSK9 can act as an alternative to the administration of statins [62]. However, the wide clinical use of anti-PCSK9 monoclonal antibodies is limited due to the high cost of these drugs, low availability, and insufficient base on the results of long-term clinical use [63]. However, in addition to monoclonal antibodies, several alternative therapeutic solutions associated with PCSK9 inhibition have been developed in recent years. These options include: small molecules, microRNAs (miRNAs) for PCSK9, and vaccine structures for PCSK9. At the same time, only the microRNA -based drug is currently undergoing clinical trials, and the other two therapeutic options have been used only in animal experiments, however, the results of these studies give hope for the high poten-

tial of these developments. The first anti- PCSK9 miRNA -based drug is inclerizan. Its mechanism of action is based on binding to the PCSK9 mRNA site and inhibiting the transcription of this protein, which leads to a decrease in serum PCSK9 concentration, as well as a steady decrease in LDL levels over several months, which is associated with a long half -life of the molecule and may be an advantage in comparison. with monoclonal antibody therapy [64]. The efficacy and safety of this drug have been shown in phase I and II clinical trials. According to the results of these studies, two or even one dose of inclerizan per year was sufficient to sustainably lower LDL cholesterol levels and improve the overall lipid profile [65,66]. Another alternative approach to the use of antibodies could be vaccination, which has the advantage of lower cost and less frequency of administration [67]. A vaccine containing components of the PCSK9 molecule is aimed at inducing the body's own antibodies that bind and inhibit the action of the PCSK9 protein. The effectiveness of this method has been shown in various studies on animal models. Vaccination with PCSK9 resulted in improved lipid profile for up to 40 weeks, reduced inflammation and total cholesterol levels [68,69]. The third alternative to the use of monoclonal antibodies can be the use of small molecules—PCSK9 inhibitors. Their potential advantages are better safety, low cost and ease of production [70]. An example of such a molecule is P-21, which has shown high bioavailability and effectiveness in lower-



**Fig. 1. The main mechanisms of action of PCSK9 inhibitors.** (A double-edged yellow arrow means the interaction of molecules, a red cross means a disruption of molecular interaction or protein translation, a yellow down arrow means the next stage of the process, a red up arrow and a green down arrow mean an increase and decrease in the LDL content in the plasma, respectively, multidirectional blue arrows mean the destruction of LDL in the lysosome.) PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low-density lipoprotein receptor; miRNA, microRNA.

ing LDL levels [71]. The main mechanisms of action of PCSK9 inhibitors are shown in Fig. 1.

#### New ANGPTL3 Inhibitors

Angiopoietin-related protein 3 (ANGPTL3) is one of the new therapeutic targets in the treatment of dyslipidemia. ANGPTL3 inhibitors are being developed to reduce plasma LDL cholesterol and triglyceride levels. ANGPTL3 is a liver-secreted factor that inhibits lipoprotein lipase through the formation of a complex with the related protein ANGPTL8 [72]. A promising treatment option is the use of specific monoclonal antibodies. Thus, an antibody targeting the C-terminal LPL inhibitory domain of ANGPTL3, Evinacumab, was developed. In a phase 3 clinical trial, 24 weeks of treatment with evinacumab resulted in significant reductions in LDL cholesterol (47%), HDL cholesterol (30%), and triglycerides (55%) in patients with homozygous familial hypercholesterolemia [73]. Another promising strategy is the use of genome editing systems. A study [74] using the C57BL/6 mouse model demonstrated that knockdown of the *Angptl3* gene in mouse liver by administration of lipid nanoparticles carrying CRISPR associated protein 9 (Cas9) mRNA and *Angptl3* genome editing guide

RNA resulted in significant reductions in serum ANGPTL3 protein, low-density lipoprotein cholesterol, and triglyceride content. Moreover, the therapeutic effect persisted for 100 days after administration of a single dose of the drug. Just like for the protein target PCSK9, the development of vaccines targeting ANGPTL3 is promising. A study [75] showed that administration of a virus like particles (VLP) vaccine targeting ANGPTL3 resulted in decreased triglyceride levels in mice.

#### New CETP Inhibitor

Cholesteryl ester transfer protein (CETP), which is a glycoprotein, mediates the bidirectional transfer of cholesteryl esters and triglycerides between HDL and LDL [76]. It is known that a decrease in CETP activity causes an increase in the level of HDL to LDL and a decrease in the risk of developing atherosclerotic lesions. In view of this, CETP seems to be a promising target for the development of drugs against atherosclerosis, but many drugs under development do not provide the desired effectiveness [76]. Obicetrapib is one of the most successful CETP inhibitors, showing efficacy in clinical trials of sudden dyslipidemia when detected with statins [77,78]. In clinical trial [77],

combining obicetrapib with ezetimibe while taking a statin reduced LDL cholesterol to <100 mg/dL in 100% of participants in the combination therapy group and <55 mg/dL in 87% of participants. No side effects were observed when taking obicetrapib. In clinical trial [78], treatment with obicetrapib while taking statins led to a significant decrease in LDL cholesterol (up to 51%), apolipoprotein B (up to 30%), and also led to an increase in HDL cholesterol (up to 165%) in the placebo group, in which patients used only statin treatment.

## Discussion

Since dyslipidemia is one of the key factors in the pathogenesis of atherosclerosis, as well as a number of other cardiovascular diseases, the study of the features of its initiation and progression is an important step in the fight against this type of disease. Thus, in our opinion, a more detailed study of the role of molecular modifications of LDL in the progression of atherosclerosis and the development of dyslipidemia, in particular, is required. Using the example of the development of PCSK9 inhibitors, it can be understood that the identification of new protein “amplifiers” of dyslipidemia creates a prerequisite for the development of a whole group of various types of drugs aimed at the identified pathological target. Thus, another example of such a target is the adenosine triphosphate (ATP)- citrate lyase enzyme and its inhibitor, bempedoic acid [79]. As can be seen from the previous section, the use of new types of drugs has increased bioavailability, reduced side effects and frequency of administration. It is also worth noting that the identification of enzymes whose activity is associated with the progression of dyslipidemia will allow us to discover new ways of the pathogenesis of atherosclerosis.

## Conclusions

LDL and VLDL are one of the key players in the development of dyslipidemia, initiation of endothelial wall damage, accumulation of cholesterol, attraction of adhesion molecules, chemokines and immune cells to the wall of the damaged vessel and the subsequent development of atherosclerotic lesions. One of the main ways to treat dyslipidemia at present is the use of drugs based on statins, as well as monoclonal antibodies—PCSK9 inhibitors. At the same time, traditional drugs have a number of disadvantages, including low bioavailability, risk of severe side effects and high price. The use of new delivery systems (nanoparticles for statins) and the development of new types of PCSK9 inhibitors can solve these problems. In addition, other drugs for the treatment of dyslipidemia are being developed, aimed at new targets, such as bempedoic acid.

## Author Contributions

AO and VS designed the review plan. IS and VG did the interpretation of data for the work. AB and EP wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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