Review Article

Interventional Cardiology

ApoB: The way from atherogenic component to biomarker and therapeutic target

Abstract

There are numerous mechanisms involved in the development of atherosclerosis. While most available methods for the diagnosis, prevention, and treatment of the disease are based on LDL-C management, there is a strong need for alternative strategies that could be used in cases where standard treatment practices are not efficient enough. ApoB plays a critical role in atherogenesis. Being an important constituent of lipoproteins, ApoB promotes the retention of atherogenic particles in the arterial intima, thus contributing to the initiation and progression of the disease. In this review, we will look into the mechanisms through which ApoB is involved in atherogenesis to reveal alternative diagnostic methods based on the plasma ApoB levels which can be used as a biomarker indicating cardiovascular risk. In the last section of the paper, we will consider possible therapeutic strategies for the prevention and containment of atherosclerosis based on the downregulation of ApoB levels and suppression of its synthesis.

Keywords: ApoB • Atherosclerosis • Apolipoprotein

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Introduction

Characteristics and structure of ApoB

Apolipoproteins are the protein components of lipoproteins bound to their surface. They are, to a large extent, determining the functions of the lipoproteins, their metabolism, and transport. Apolipoprotein B (ApoB) is an important constituent of chylomicrons and their remnants, as well as Very-Low-Density Lipoproteins (VLDLs) and their metabolites, including Intermediate-Density Lipoproteins (IDLs) and Low-Density Lipoproteins (LDLs). Additionally, the ApoB particle plays crucial role in maintaining the lipoprotein's structure, serving as a frame for the lipoprotein [1].

ApoB can be found in two forms: The full-length ApoB100, which consists of 4536 amino acids, and ApoB48 containing only the N-terminal 2152 amino acids. Both forms are encoded by the APOB gene, however, their physiological impact varies. Human ApoB48 can be observed in chylomicrons and their remnants and is mainly generated and released within the intestine, while ApoB100 is primarily expressed in the liver, being an essential constituent of VLDL, IDL, and LDL [2]. Thus, the latter has more clinical relevance when it comes to evaluating blood atherogenicity. Of all the plasma apolipoproteins, ApoB100 cannot transfer from one lipoprotein to another. It has a larger size compared to other apolipoproteins and has relatively low hydrophobicity [3].

The ApoB polypeptide consists of five domains: βα1, β1, α2, β2, and α3, where α mostly represents an α-helical structure and β–a β-sheet structure. The N-terminal sequence plays an essential role in the VLDL formation as it interacts with the Microsomal Triglyceride Transfer Protein (MTP). The first step in ApoB synthesis is

the transfer of cholesterol esters, phospholipids, and triglycerides to the ApoB particle, mediated by MTP in the Endoplasmic Reticulum (ER). Lipoproteins are bound to the original ApoB particle by the β-sheet domains anchored to the lipid core. Just like in other apolipoproteins, an amphipathic α-helix domain lies between the two β-sheet domains [4]. ApoB100 has unique amphipathic properties due to the β-sheet domain's elongation around the lipoprotein. This quality allows the establishment of strong bonds to lipids, primarily those within the core of the lipoprotein. The integrity of LDL particles is largely determined by these lipid-associating regions [5].

ApoB100 is synthesized by the ribosomes on the ER surface. Then it is transported to the ER lumen. Secretion of ApoB100 is mainly regulated during its post-translational modification. Although secretory proteins synthesized on the ER surface are typically quickly translocated through the membrane to the ER lumen, ApoB100 attaches to the ER membrane right after the post-translational stage begins [6]. Thus, the nascent peptide is exposed to the cytosol. As a result, 50%-80% of the newly synthesized protein is degraded by hepatocytes, which determines how much ApoB100 is secreted by the cells [7].

The secretion or degradation of the newly synthesized ApoB100 also depends on the availability of main lipoprotein lipids, phospholipids, cholesteryl esters, and triglycerides. If there is an insufficient amount of lipids, or if MTP is impaired, the chaperone protein Binding immunoglobulin Protein (BiP) will attach to ApoB, which then will be targeted for proteasomal degradation [8,9]. Post-translational degradation of ApoB, which happens independently of the proteasome, has also been observed. ApoB100 translocation, as well as its synthesis and secretion, is predominantly determined by MTP and the availability of lipids. During the ApoB100 translocation through the ER, MTP mediates the lipid transfer and the formation of the polypeptide while it is transferred from the ribosome to the ER lumen. ApoB secretion can be suppressed *via* MTP inhibition. ApoB maturation takes place in the Golgi apparatus before it is secreted from the hepatocyte [10]. The size of the secreted VLDL is largely defined by the number of triglycerides added in the Golgi apparatus, and thus the availability of triglycerides in the hepatocytes plays an important role in VLDL assembly. Excess of triglycerides caused by such conditions as untreated diabetes, obesity, or a diet containing a lot of simple carbohydrates, promotes the synthesis of VLDL rich in triglycerides. The levels of triglyceride-rich large VLDL particles, as well as chylomicrons, are higher after a high-fat meal. The availability of triglycerides affects both the size and the density of particles containing ApoB. Lipoprotein secretion can be also affected by other factors, including the availability of fatty acids and insulin [11].

In humans, most of the circulation ApoB-containing lipoproteins are absorbed and degraded in the liver. The uptake is mediated by three main receptors: Heparin sulfate proteoglycans, Scavenger Receptor class B type I (SR-BI), and the LDL Receptor (LDL-R). The half-life of the LDL-R is around 25 hours, and it is responsible for the uptake of over ⅔ of normal LDL. LDL-R binds to a particular site in the α3 domain of ApoB100 [12]. Site B is the main binding region interacting with the LDL-R, which is located at residues 3356–3368. ApoB100 is bound to the LDL receptor only after a conformational change of the polypeptide, which occurs through the lipolysis of VLDL to LDL. Loss-of-function mutations of the LDL-R or in ApoB can lead to familial hypercholesterolemia, which is manifested by extremely high LDL levels in the blood, thus promoting the early development of atherosclerosis [13]. In addition, gain-of-function mutations in Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9), which promotes LDL-R degradation, also lead to elevated LDL levels. LDL is separated from the LDL-R after endocytosis. The LDL, which has a long half-life of between 2 and 3 days, is transferred to the lysosomes and targeted for degradation, and its lipid cargo is released. The majority of LDL-Rs are transported back to the surface of the cell. Thus, ApoB plays a pivotal role in the catabolism of IDL, LDL, and VLDL as it interacts with plasma LDL receptors [14,15].

Apart from the LDL-R binding site, ApoB also has a minimum of eight possible Proteoglycan-binding (PG) sites. Two of these presumably interact with proteoglycans: Site A and site B located at residues 3148–3158 and 3359–3369, correspondingly. The same sites also bind to the LDL-R. The arginine and lysine residues of ApoB that have a positive charge interact with the negative carboxyl and sulfate groups of glycosaminoglycans through an ionic reaction allowing the ApoB- containing lipoproteins to bind to PGs [16]. The ability of ApoB100 to bind to intimal proteoglycans has a high medical significance as this is believed to be the primary cause of LDL retention in the subendothelial area. The aggregation of ApoB-containing lipoproteins in the vessel wall is largely due to the tendency of impaired or modified ApoB100 to retain in the arterial wall. Fusion and accumulation of the particles in the intima can be promoted by a change in their conformation at a molecular level caused by enzyme-induced ApoB proteolysis [17].

ApoB48, however, is mainly observed on chylomicrons and their remnants. As they do not contain any LDL-R binding domain, ApoB48 clearance predominantly occurs *via* the Heparin Sulfate Proteoglycan (HSPG) pathway. In diabetes, elevated glucose affects perlecan biosynthesis, leading to a reduction in HSPG. This results in higher levels of ApoB48-containing lipoproteins in plasma, ultimately initiating postprandial dyslipidemia. Chylomicrons have a large size and thus cannot infiltrate the vessel wall, while

their remnants may do so and thus are considered to accelerate the development of atherosclerotic lesions [18,19].

Literature Review

Metabolism of ApoB containing lipoproteins

There are two forms of ApoB, ApoB100, and ApoB48, and they have different properties. Being the main apolipoprotein in the LDL structure, ApoB100 is primarily produced by the liver, moderating the generation and secretion of triglyceride-rich VLDL. Each LDL particle only contains a single ApoB molecule. Progressive hydrolysis of triglycerides mediated by lipoprotein lipase and hepatic lipase metabolizes the circulating VLDL to LDL and cholesteryl ester-enriched IDL [20]. By contrast, ApoB48 is only synthesized in the intestine by the ApoBec-1 enzyme complex *via* an RNA editing mechanism. ApoB plays an important role in the production and expression of triglyceride-rich chylomicrons, which are essential for the absorption of vitamins and dietary fats in the intestine. Just like LDL, chylomicron metabolism is based on the hydrolysis of triglycerides by LPL and hepatic lipase. As a result of this process, the circulating chylomicrons are transformed into cholesteryl ester-enriched chylomicron remnants, which, in their turn, provide an energy source for the tissues by expressing fatty acids [21].

VLDL synthesis, its transformation to LDL, and the LDL-R-mediated LDL clearance can be reflected by the static measurements of cholesterol in the LDL pool. LDLR gene mutations are the main cause of Familial Hypercholesterolemia (FH), an autosomal dominant-inherited disorder characterized by high LDL-C levels and an elevated risk for cardiovascular events [22]. ApoB serves as a ligand that allows the LDL-R clearance of LDL in the liver. In contrast, ApoE is involved in the clearance of IDL and chylomicron remnants, which occur either *via* the remnant receptor pathway or through the LDL-R. The remnant receptor pathway was discovered because subjects with homozygous FH and thus an impaired LDLR function have extremely high LDL-C levels but normal levels of triglycerides in their blood. To clean these remnant lipoproteins, they need to bind to LDLR-like protein -1 and heparin sulfate proteoglycans in the hepatic space of Disse. This process is commonly referred to as secretion capture and requires local enrichment through ApoE expression in the liver [23].

ApoB in atherogenesis

The following model provides more clarity on the association between the risk for atherosclerosis and the number of ApoB lipoproteins and explains why their number is more significant than the amount of cholesterol within them. The amount of ApoB particles in the artery lumen indicates how many ApoB particles enter the vessel wall and their retention rate in the subintimal area. The number of ApoB particles in the artery lumen correlates directly with the number of particles that are to penetrate the intima and, subsequently, with the number of ApoB particles that will be retained in the vessel wall, unless other factors interfere. However, the size of ApoB particles may affect their ability to enter the intima. Thus, smaller particles that contain less cholesterol penetrate the artery wall more often and are more prone to attach to the glycosaminoglycans within the intima, compared to large particles with higher cholesterol content [24]. This means that more small particles with low cholesterol content will be retained in the subintimal area even if an equal number of large and small particles enter the artery wall. On the other hand, the amount of cholesterol within the particle trapped in the subintimal area corresponds to the amount of cholesterol that will be released and potentially can damage the artery wall, and larger particles contain more cholesterol. As a result, all LDL particles of all sizes are more or less equally dangerous as they pose an equal per-particle risk [25].

Ference, et al. [26], has demonstrated that VLDL particles are as atherogenic as LDL. However, there are always far more LDL particles than VLDL, so the total risk from the LDL fraction is much greater. Thus, there is a more direct association between cholesterol and cardiovascular risk than between triglycerides and cardiovascular risk, although patients with Cardiovascular Disease (CVD) more often have hypertriglyceridemia than hypercholesterolemia.

It is worth mentioning that ApoB particles are not always equally atherogenic. Firstly, in type III hyperlipoproteinemia, there is a significantly higher amount of ApoB48 and ApoB100 remnant particles with abnormally high cholesterol content, which results in much greater damage per particle than otherwise. The concentrations of particles are also 20 to 40 times greater than in subjects without the disorder. This condition cannot be diagnosed based on the conventional lipid panel, which limits the current practice to a significant degree. However, the disorder can be identified from the amount of total cholesterol, triglycerides, and ApoB [27,28].

Secondly, there is ample evidence that Lipoprotein(a) (Lp(a)) is an important and independent risk factor for CVD and plays a key role in the development of aortic stenosis. A recent meta-analysis showed that Lp(a) could cause a high risk for cardiovascular events despite statin therapy. Sub- analyses from studies assessing the results of PCSK9 inhibitor therapy reported that even subjects with LDL-C levels close to normal were presented with higher cardiovascular risk because of Lp(a). As for patients with FH, elevated Lp(a) levels increased the risk even further [29].

Thirdly, differences in the structure of glycosaminoglycans and other constituents of the artery wall might affect ApoB's binding

ability and increase the number of trapped particles. Therefore, the notion that glycated ApoB particles are more prone to binding, deserves further consideration [30].

Finally, the intensity of the innate and acquired immune responses to trapped ApoB particles varies between individuals. Thus, the degree of inflammation-induced damage to the artery wall is also different [31].

As a result, the scenario that takes place once the ApoB particle has entered the arterial wall, explains the individual variance of the per particle risk. However, the amount of ApoB that enters the artery wall depends on the ApoB concentration in the vessel lumen [32].

ApoB as biomarker

Approximately 50% of all subjects with chronic coronary syndrome are at high risk for cardiovascular events despite having normal cholesterol levels on standard lipid profiles. Thus, ApoB and non-HDL-C are the main up-and-coming biomarkers [33].

Every atherogenic particle contains one ApoB molecule, making ApoB the most promising biomarker of high risk for cardiovascular events. By contrast, standard LDL-C reflects lipid concentration in a fraction of heterogeneous particles with various densities, sizes, and lipid content. LDL particles usually contain more than 90% of the total ApoB. On the other hand, LDL particles may have different lipid content, which is why there is no strong association between these values and LDL-C concentrations [34]. According to recent studies, ApoB is a more precise biomarker of cardiovascular events, including myocardial infarction, irrespective of age or gender. A study carried out among Japanese patients with diagnosed recurrent CAD identified *via* coronary artery stenosis over 75% on coronary angiography, reported that individuals with elevated ApoB levels in plasma presented with more advanced plaques, a greater percentage of necrotic core and higher length of the lesions on a virtual-histology intravascular ultrasound of the culprit lesions, compared to individuals with low ApoB levels in plasma. There was observed no association between ApoA1 levels and the necrotic core volume in the assessed lesions. The study confirmed the advantage of ApoB as a biomarker of high necrotic core volume and a potential predictor of unstable plaque, compared to LDL-C [35,36].

Statins, which currently are one of the main lipid-lowering agents, provide a markedly greater decrease in LDL-C than in ApoB concentrations. This discrepancy indicates a need for more sensitive and specific methods of regular lipid monitoring [37].

Moreover, ApoB can be used to measure the risk of Major Cardiovascular Events (MCVE) in individuals with LDL-C levels lower than the median, irrespective of whether the atherogenic particles are primarily represented with LDL-C, or not. This property of ApoB is highly significant for medical practice, especially in diabetic patients where plasma atherogenicity is more dependent on other lipoproteins than LDL-C, for example, triglycerides [38]. ApoB includes not only LDL-C, but also lp(a), VLDL-C, and IDL-C, and this property largely accounts for its high capability of predicting the risk for MCVE, as all these particles can be highly atherogenic and should be considered when evaluating the cardiovascular risk. Additionally, ApoB reflects the number of atherogenic particles rather than cholesterol levels which can vary between different particles because of lipid metabolism [39].

Although the transition to the standard measuring of ApoB has certain drawbacks, primarily higher cost and impracticality, and thus are met with hesitancy among clinicians, it allows precise measurement of lipoproteins aside from LDL-C and thus can be critical in cardiovascular risk management. It would also help to reduce CVD-related morbidity and mortality in some groups of patients, especially those with diabetes. Furthermore, measuring ApoB levels can be essential for identifying atherogenic dyslipoproteinemias, including remnant lipoprotein disorder [40].

Immunoassay costs a lot and is not time-efficient. In addition, it may have different accuracy. An alternative method of estimating circulating ApoB is to use an algorithm. However, these data have doubtful clinical relevance as they are only approximations derived from such variables as total cholesterol and LDL or HDL, as well as triglycerides [41].

deVries, et al. [42] have revealed that if ApoB-containing lipoproteins bind to circulating erythrocytes, which can be identified using flow cytometry, cardiovascular mortality is lower. This negative correlation between the degree of erythrocyte-ApoB binding, and atherosclerosis deserves further attention as another way to use ApoB as a biomarker.

ApoB as a target of CVD treatment

Although ApoB can be considered a potential target in CVD prevention and risk management, there are few therapeutic methods aimed at regulating its level. A recent study reported that subjects, who have autoantibodies that suppress ApoB directly, demonstrate lower CVD prevalence. Specifically, a 45% lower risk of MI was reported in patients with high levels of antibodies that are targeted at native peptide 210 of the protein. These findings indicate that apart from being an important biomarker, ApoB can also be considered a therapeutic target in CVD treatment [43].

The lipid constituents of lipoproteins are constantly being exchanged between classes. The lipid metabolism pathway is largely dependent on Cholesteryl Ester Transfer Protein (CETP). It is a hydrophobic glycated protein involved in the exchange of triacylglycerol and cholesteryl esters between ApoB-containing lipoproteins and HDL. CETP promotes the formation of

lipoprotein particles like VLDL, which are rich in triglycerides and contain ApoB. This protein is in a negative correlation with the size and structure of HDL particles [44]. Thus, it is considered atherogenic. CETP inhibitors were therefore expected to increase HDL-C concentrations and decrease ApoB-rich particles, such as LDL-C, reducing the cardiovascular risk. However, the first trials provided somewhat unexpected results. The trial in humans involved four CETP inhibitors, including evacetrapib, torcetrapib, dalcetrapib, and anacetrapib, of which only the latter slightly reduced the cardiovascular risk, while others were either neutral or increased the cardiovascular risk [45]. During phase 3 of a Randomized Placebo-Controlled Trial (REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid-Modification), anacetrapib led to a 9% relative reduction in risk for MCVE. The experiment involved patients with pre-existing atherosclerosis following a 4-year median treatment period [46]. This action of anacetrapib can be explained by its LDL-C decreasing activity and reduction in ApoB-containing lipoprotein particles, as well as its VLDL-lowering effect. Anacetrapib can also promote clearance of ApoB-containing lipoproteins by increasing the amount of cell surface LDL-Rs. A major side effect of this drug is that it may cause excess lipid retention in adipose tissues. Thus, the development of anacetrapib could not be continued, although there is a need for more research on therapeutic mechanisms targeting CETP [47]. In 2019, Ference, et al. [48] carried out a study involving 654,783 people, of which 91,129 were diagnosed with Coronary Heart Disease (CHD), and concluded that both LDL-C-lowering LDLR-gene variant and triglyceride-lowering lipoprotein lipase gene decreased the risk for MCVE to a similar extent if measured by an absolute change in ApoB. This finding proved that CHD risk is primarily related to the number of ApoB-containing lipoprotein particles rather than the amount of cholesterol in each LDL particle. Thus, treatment methods aimed at reducing LDL-C levels by decreasing cholesterol content in each particle without downregulating the number of particles will not be effective, despite a decrease in LDL-C in the lipid profile.

Niacin, a vitamin of the B-complex, is a well-known agent used for the regulation of plasma levels of lipids and lipoproteins, as well as for the treatment of atherosclerosis. The drug helps to downregulate circulating triglycerides and ApoB-containing lipoproteins, like LDL and VLDL, and has two main mechanisms of action. Firstly, it reduces free fatty acid mobilization that takes place in adipose tissues. Secondly, niacin inhibits hepatocyte diacylglycerol acyltransferase–2, which is involved in triglyceride production [49]. When the availability of triglycerides decreases, it accelerates ApoB degradation within the liver cells, which results in lower hepatic secretion of LDL and VLDL. Niacin is almost as efficient as statins when it comes to regulating lipid metabolism as it improves several parameters. Unfortunately, the use of this agent is limited because of some adverse effects, such as flushing. This side effect might be suppressed by laropiprant, a prostaglandin D2 receptor antagonist that reduces flushing. Combined in a fixed-dose tablet, these drugs allowed to improve the lipid profile in subjects with primary hypercholesterolemia or mixed dyslipidemia, thus mitigating the CHD risk [50,51].

Another group of drugs is PCSK9 inhibitors, such as alirocumab and evolocumab, both of which have been established as safe and effective agents aimed at regulating LDL-C levels. These human monoclonal antibodies are used in the treatment of primary hyperlipidemia and have been reported to reduce stroke and MI in subjects with diagnosed CVD. The mechanism of action is based on the suppression of PCSK9 enzyme activity, which promotes LDL-R degradation [52]. Thus, these drugs stimulate LDL-R accumulation, resulting in enhanced clearance of ApoB-containing lipoproteins, as well as a lower amount of ApoB particles and LDL.

Besides the monoclonal antibodies (alirocumab and evolocumab), another approach to PCSK9 inhibition is currently under investigation. Inclisiran, which is the small interfering RNA molecule, can also lower the level of LDL-C, and, what is more important in the scope of our review, reduce the ApoB levels by approximately 4%-40% [53].

Current guidelines suggest the administration of PCSK9 inhibitors following ezetimibe treatment in case the target LDL-C level has not been reached after treatment with the maximum tolerated statin dose [54,55].

Inhibiting the synthesis of ApoB may be a successful therapeutic strategy against CVD as it would result in lower LDL-C and VLDL-C levels. Furthermore, ApoB is involved in LDL-C-related endothelial dysfunction, suggesting that ApoB inhibition may be an effective therapeutic approach in treating ischemic CVD. Antisense oligonucleotide technology has been proposed as one of the strategies for ApoB reduction [56]. A 20-base-pair single-stranded DNA oligonucleotide binding to the specific mRNA sequence which encodes human ApoB-100, mipomersen, showed very good results in human trials. However, it will not be developed further due to its side effects, including liver toxicity. In addition, mipomersen suppresses CYPP3A4 and thus cannot be used in patients administered other drugs metabolized by this enzyme [57].

Lomitapide is an oral MTP inhibitor with a hepatic mechanism of action based on binding to MTP in the ER of enterocytes and hepatocytes. MTP plays an important role in VLDL synthesis as it promotes the transfer of triglycerides to the ApoB particles within hepatocytes. By binding to MTP, Lomitapide suppresses VLDL formation leading to a reduction in the amount of secreted ApoB-containing lipoproteins [58]. The drug is only used in patients with homozygous FH in combination with a low-lipid diet and

other treatment methods aimed at decreasing lipid levels. Due to its numerous side effects, including elevated transaminases and gastrointestinal adverse actions, the drug has limited tolerability and use [59].

Another drug that has surprisingly been found to reduce ApoB levels by up to 7% is dabigatran, a small-molecule anticoagulant administered orally. The agent binds competitively and selectively to the active site on thrombin and is administered for the prevention of stroke in atrial fibrillation. The exact ApoB-lowering mechanism of this therapy has not been revealed yet [60]. However, Joseph, et al. [61], suggested that it may be explained by the competing activity of microsomal carboxylesterases. Its ApoB-lowering action may also shed light on the efficacy of dabigatran in reducing the risk of stroke. Further examination of the drug's mechanism of action may provide additional proof of the importance of ApoB regulation in the treatment of hyperlipidemia.

Bempedoic acid inhibits hepatic ATP citrate lyase, which exerts its effect upstream of HMG CoA reductase. The inhibition of this enzyme suppresses intracellular cholesterol formation and upregulates LDL-R on the liver cells, resulting in enhanced hepatic LDL uptake and reduction in the levels of circulating LDL-C, VLDL-C, and ApoB [62].

Angiopoietin-Like Protein 3 (ANGPTL3) inhibition is another therapeutic strategy used in CVD treatment. ANGPTL3 is a secretory glycoprotein that reversibly suppresses the catalytic function of lipoprotein lipase, an enzyme involved in the hydrolysis of triglycerides. A human IgG monoclonal ANGPTL3 antibody, evinacumab, promotes the catabolism of VLDL, thus reducing VLDL, LDL, and triglyceride levels [63]. The drug enhances the clearance of ApoB-containing lipoproteins which subsequently decreases ApoB levels. The drug was recently included in the list of FDA-approved medications for homozygous FH treatment and can be administered in combination with other LDL-C-lowering therapies [64].

Several agents with primary targets other than ApoB can incidentally decrease ApoB levels. For instance, fibrates aimed at plasma triglycerides reduction by suppressing their synthesis in the liver, may also reduce ApoB concentrations by 10-20%. Another example is Gemcabene, a lipid-lowering drug that is currently being developed. Its mechanism of action is based on ApoC-III reduction resulting in enhanced VLDL clearance. Gemcabene was also found to reduce ApoB levels as well as c-reactive protein and LDL-C.

Discussion and Conclusion

In this review, we described the role of ApoB in the initiation and development of atherosclerosis and subsequent CVD.

The analyzed data allowed us to conclude that the amount of circulating ApoB-containing particles is directly associated with blood atherogenicity and risk for atherosclerosis. Thus, apoBApoB may be effectively used as a more precise and specific biomarker indicating cardiovascular risk than standard lipograms. This approach might be particularly useful in cases when blood atherogenicity is mostly due to particles other than LDL, or the cardiovascular risk is high despite normal LDL-C levels.

Additionally, we reviewed potential treatment strategies aimed at ApoB reduction. According to several trials, decreasing ApoB may be an effective measure for atherosclerosis prevention and treatment. However, most of the currently available drugs have limited use due to their adverse actions. This finding indicates the need for further research in this field in order to establish effective therapeutic strategies and new methods for CVD risk management and treatment.

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Conflicts of Interest

The authors declare no conflict of interest.

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