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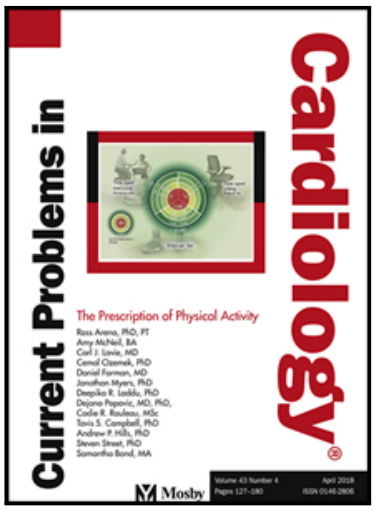

Lipid Lowering Therapy: An Era Beyond Statins

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Title: Lipid Lowering Therapy: An Era Beyond Statins

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Abstract

Dyslipidemia, specifically elevated LDL cholesterol levels, causes atherosclerotic cardiovascular disease (ASCVD) and increases the risk of myocardial infarction and stroke. Statins, a class of drugs that exert

their effects by inhibiting HMG-CoA reductase, a key enzyme in the synthesis of cholesterol, have been the mainstay of therapy for the primary prevention of cardiovascular disease and lipids reduction. Statins are associated with side effects, most commonly myopathy and myalgias, despite their proven efficacy. This review explores non-statin lipid-lowering therapies and examines recent advances and emerging research. Over the previous decades, several lipid-lowering therapies, both as monotherapy and adjuncts to statin therapy and lipid-targeting gene therapy, have emerged, thus redefining how we treat dyslipidemia. These drugs include Bile acids sequestrants, Fibrates, Nicotinic acid, Ezetimibe, Bempedoic acid, Volanesoren, Evinacumab, and the PCSK 9 Inhibitors Evolocumab and Alirocumab. Emerging gene-based therapy includes Small interfering RNAs, Antisense oligonucleotides, Adeno-associated virus vectors, CRISPR/Cas9 based therapeutics, and Non-coding RNA therapy. Of all these therapies, Bempedoic acid works most like statins by working through a similar pathway to decrease cholesterol levels. However, it is not associated with myopathy. Overall, although statins continue to be the gold standard, non-statin therapies are set to play an increasingly important role in managing dyslipidemia.

1. Introduction

Heart disease is the leading cause of death in the United States. [1] In recent years, an increasingly sedentary lifestyle and the rise of the obesity epidemic have only exacerbated disease rates. As a result, more people have been presenting to the Emergency Room with angina in recent years than ever before. In addition, the influx of myocardial infarctions and other cerebrovascular events related to significantly elevated low-density lipoprotein (LDL) levels has resulted in an increasing economic burden on the healthcare system. [2] Elevated LDL results in a phenomenon known as atherosclerosis in which high levels of cholesterol deposit in various arterial systems throughout the body. The deposition of LDL in the coronary vessels and carotid arteries increases the risk of myocardial infarction and stroke.1 While the list

of LDL lowering medications has increased in the last few years; statins have remained a mainstay of lipid-lowering therapy.

Risk Factors for Atherosclerosis

Although a poor lifestyle is a common risk factor for the development of atherosclerosis, certain rare diseases lead to higher-risk patient populations. These diseases include familial hypercholesterolemia, familial hypertriglyceridemia, abetalipoproteinemia, and the rarest, Tangiers disease. Patients typically require a more aggressive lipid suppression medication regimen and clinical follow-up to ensure a response to therapy and prevent plaque buildup and subsequent cardiovascular events.[1]

Statin Efficacy

Statins have been the mainstay treatment for the primary prevention of cardiovascular disease for several decades, following the advent of lovastatin in 1987, the first commercially available statin.[3] Statins competitively inhibit HMG-CoA reductase, a key rate-limiting enzyme in the cholesterol synthesis pathway, thereby reducing cholesterol synthesis in the liver. [4] In response to reduced hepatic cholesterol levels, hepatocytes upregulate the synthesis of LDL receptors, leading to increased LDL uptake and cycling and decreased serum LDL levels. [4,5] This reduction in serum LDL levels is the predominant pathway by which statin therapy reduces the cardiovascular burden and improves outcomes. [6] One early study examined a dose-dependent decrease of LDL cholesterol - ranging from 25 to 60% - following atorvastatin therapy. [7] Numerous studies have examined the role of statin therapy in reducing rates of major vascular events. [2,8,9] The magnitude of reduction in LDL levels within patients has been well correlated with the reduction of cardiovascular events. [6,10]

Non-Statin Lipid-Lowering Drugs

Despite significant reductions in LDL levels with statin therapy, certain patients may not achieve adequate reduction or may develop adverse effects to statins, requiring additional non-statin therapies. [7,11] A 2017 update of the 2016 ACC Expert Consensus on Non-Statin Therapies included guidelines and consideration of the evidence for bile acid sequestrants, niacin, ezetimibe, and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors. [12] Beyond these major therapy classes, fibrates, bempedoic acid, volanesorsen, and various gene-based therapies have been explored as additional lipid-lowering agents. [13-16] For patients unable to tolerate statin therapy or require a further modification of lipid levels, a complex array of alternatives are available. Then, it is essential to understand the various effects of alternative therapies and the intricate medical management of lipids. In this review, we serve to describe the current state of lipid-lowering treatments, review recent advancements, and explore growing areas of research.

2. Metabolism of Lipids in the Body

Lipid contents present in the body are either produced through (endogenous pathways) or obtained from the exogenous pathway from the diet. The endogenous pathway primarily involves lipid synthesis from the liver. Here, we discuss the pathway and mechanism of lipid production, transport, and intracellular metabolism.

Exogenous Pathway of Lipid Transport

All consumed lipid-containing foods are packaged into the hydrophobic core of chylomicrons in the small intestine. The packaging process requires interaction with ApoB48, an apolipoprotein. [17] Once chylomicrons are released into circulation; they receive ApoC-II and ApoE from the HDL molecule. Chylomicron interaction with HDL transfers cholesterol esters from HDL to chylomicrons via the CETP protein. Fatty acids in the chylomicrons are hydrolyzed by lipoprotein lipase (LPL) by using ApoC-II as a cofactor. The resulting chylomicron remnant is ultimately cleared by hepatocyte receptors. [18]

Endogenous Pathway of Lipid Metabolism

The endogenous pathway begins with VLDL synthesis by the hepatocytes. VLDL particle lipidation occurs by microsomal triglyceride transfer protein (MTP) and subsequent interaction with ApoB-100, C-II, and E on the VLDL surface to form a complete VLDL molecule. VLDL interaction with LPL then releases fatty acids into the circulation, which ultimately deposit in muscle tissue and adipocytes. [19] The VLDL core becomes IDL. The transfer of cholesterol esters from the HDL to IDL by CETP protein and interaction with hepatic lipase results in LDL formation. The newly formed LDL takes up cholesterol in the tissues and eventually ends up back in the liver via clathrin-mediated endocytosis in the hepatocytes. [17]

3. Statin Lipid-Lowering Therapy

Mechanism of action

Statins are competitive HMG-CoA reductase inhibitors in the mevalonate synthesis pathway. Decreased production of mevalonate results in reduced cholesterol production, thereby reducing the likelihood of cholesterol buildup resulting in atherosclerosis. Statins work primarily on the endogenous pathway of lipid metabolism rather than the exogenous pathway. [20] Statins have also been attributed to maintaining plaque stability, preventing clot formation, and improving blood vessel endothelium function through this mechanism. [11]

Statin intolerance

Although statins provide significant benefits in serum LDL reduction, adverse effects can occur. Approximately 15% of patients develop myalgias. [11] Because of such effects, patients might not be compliant with medication. However, in the SAMSON trial, patients in the placebo group also

experienced myalgias, attributed to the placebo effect from widespread knowledge of statin adverse effects. [20] Rhabdomyolysis is a rare adverse effect in 0.1% of statin users. If untreated, rhabdomyolysis can result in acute tubular necrosis, which may be fatal. Still, rhabdomyolysis continues to have an incidence of 0.4 per 10,000 statin users, which makes it a very rare incidence. [11]

4. Non-Statin LDL Cholesterol-Lowering Therapy (Bile acids sequestrants, Ezetimibe, Bempedoic Acid)

Bile acids sequestrants

Mechanism of action

Bile acids are byproducts of hepatic cholesterol breakdown. Cholesterol conversion to bile acids accounts for a considerable daily cholesterol turnover. Bile acid synthesis produces bile flow and biliary secretion of bile acids, phospholipids, cholesterol, medications, and toxic metabolites. Cholic acid (CA) and chenodeoxycholic acid (CDCA), the two main bile acids generated in the liver, are conjugated with taurine or glycine for bile secretion. Bile salts retained in the gallbladder form mixed micelles with phospholipids and cholesterol before being released into the colon to promote digestion and nutritional absorption. Released bile acids are primarily reabsorbed in the ileum and returned to the liver via the portal circulation, obstructing bile acid synthesis. [21]

Bile acid sequestrants are strongly positively charged molecules that adhere to negatively charged bile acids in the stomach, diminishing their lipid solubilizing activity and, as a result, limiting cholesterol absorption. The bile acid sequestrants reduce bile acid reabsorption and, subsequently, total body stores of bile acids, which results in increased cholesterol utilization for bile acid production and decreased serum cholesterol levels.[12,22] Cholestyramine, colesevelam, and colestipol are three bile acid sequestrants authorized by the US Food and Drug Administration (FDA) to treat hypercholesterolemia.[12] Colextran, approved for use in Spain and Italy, and Colestilan, approved in Japan, are other bile acid sequestrants.

(a) Cholestyramine, commercialized under the names of Questran, Efensol, Prevalite, Ipocol, Vososan, and Quantalan, was the first bile acid sequestrants to be approved by the FDA in 1973. The therapeutic dosage is 12–27 grams per day. [23] In the Lipid Research Clinics Coronary Primary Prevention Trial, cholestyramine reduced LDL cholesterol levels by 12.6% compared to placebo. Compared to the control group, cholestyramine resulted in a 19% reduction in the combined end outcome (i.e., coronary heart disease death, nonfatal myocardial infarction, or both) in men at high risk for coronary heart disease. [24]

(b) Colestipol, commercialized under the trade names Colestid, Lestid, and Cholestabyl, was approved by the FDA in 1977. The therapeutic dosage is 5–30 grams per day. [23] One study found that patients with typical phenotypes of hyperlipidemia who were given 5 g of colestipol hydrochloride three times daily achieved an average reduction in cholesterol levels of 40 mg/100 ml (14%). [25]

(c) Colesevelam, commercialized under the trade names Welchol and Cholestagel, was approved by the FDA for use in 2000. The therapeutic dosage is 3.8-4.4 grams daily.23 494 individuals with primary hypercholesterolemia were assigned to receive placebo or colesevelam (2.3 g/d, 3.0 g/d, 3.8 g/d, or 4.5 g/d) for 24 weeks in a double-blind, placebo-controlled study conducted in 1998. Colesevelam lowered mean LDL levels by 18% without significant side effects. [26]

In general, bile acid sequestrants are usually reserved for those patients who do not respond to dietary modifications or exercise therapy first; however, they may be used in conjunction with the therapy.12 They also have an additional benefit for patients experiencing cholestatic pruritis. [27]

Pharmacokinetics

Bile acid sequestrants are neither absorbed nor metabolized; instead, they bind to bile acids in the small intestine and are eliminated in the stool. Because bile acid sequestrants are not systematically absorbed,

primary interactions with other molecules occur in the intestines. The sequestrants can interact with fat-soluble substances, including fat-soluble vitamins, and interfere with absorption. [28]

Pleiotropic effects

Besides cholesterol-lowering effects, bile acid sequestrants have demonstrated therapeutic non-lipid lowering effects. These pleiotropic effects include improved non-cholesterol lipid metabolism, glucose metabolism, energy metabolism, and additional anti-inflammatory and anti-thrombotic effects. [29] Due to lack of systemic absorption, bile acid sequestrant adverse effects are specific to the gastrointestinal tract. The most common side effects include nausea, vomiting, abdominal pain, and constipation. [12] Additionally, as previously described, malabsorption of the fat-soluble vitamins A, D, E, and K may occur, so that supplementation may be recommended for patients on the medication. Elderly Patients seem to be more at risk of developing these adverse effects than the younger demographic. Therefore, patients should be closely monitored to ensure LDL levels remain in appropriate ranges, to address adverse effects, and exacerbating pleiotropic effects, do not occur.

Ezetimibe

Mechanism of action

Ezetimibe does not alter cholesterol and triglyceride absorption like statins or other lipid-lowering drugs. Instead, they act as selective inhibitors of bile and dietary absorption. [30] Ezetimibe binds NPC1L1 (Niemann-Pick C1-like 1), which inhibits the intestinal absorption of biliary and dietary cholesterol. In turn, cholesterol stays in the lumen of the small intestine and keeps going further to be excreted. [31] In many established animal models, ezetimibe reduces the cholesterol of chylomicrons as it reduces cholesterol absorption. Therefore, the amount of cholesterol that reaches the liver via chylomicrons also decreases. This ultimately leads to a decrease in plasma levels of LDL-C. In addition, although ezetimibe has not been proven to affect the level of APO-48, in some studies, it causes a decrease in the level of APO-100.

Pharmacokinetics

The absorption of ezetimibe is rapidly following oral administration since food doesn't alter its mechanism. Although the cytochrome P450 system doesn't perform its metabolism, it still undergoes extensive glucuronidation in the intestine. As a result, its elimination gets altered in the elderly and those with renal insufficiency. [32] The ezetimibe and ezetimibe-glucuronide ratio reach its maximum within a few hours (1-2 hours) following administration and completes its terminal half-life is approximately 22 hours. [33] Recommended daily oral intake dose for ezetimibe, which can be administered in the morning or evening, is 10mg.

Pleiotropic effects

The pleiotropic effects of ezetimibe remain controversial, and it is unclear whether these effects are related to LDL reduction or can be attributed to lipid-lowering-independent mechanisms. Most importantly, even if these effects exist, their clinical relevance is doubtful. [34]

Bempedoic Acid

Mechanism of action

Bempedoic acid acts by inhibiting the cholesterol biosynthesis metabolic pathway, similarly to statins. However, it is administered to patients as a prodrug, which gets converted into the active form only in the liver sparing muscles (thus no myopathy). In contrast to the HMG-CoA reductase-inhibiting action of the statins, activated bempedoic acid (coenzyme A form) functions to inhibit ATP-citrate lyase within the hepatocytes. This step of ATP-citrate lyase inhibition is upstream of the statin-targeted HMG-CoA reductase step. The major advantage of bempedoic acid over statins is the absence of myopathy associated with its use, thus becoming an alternative for patients with statin-induced myopathy. [35]

Pharmacokinetics

The median time required by bempedoic acid to reach the maximum plasma concentration (Cmax) is 3.5 hours, with a steady state taking almost 7 days. No effect of food on oral bioavailability was found. Vd or the apparent volume of distribution of bempedoic acid is approximately 18L, thus having minimalistic extrahepatic distribution. About 99 percent of bempedoic acid and its metabolites bind to the plasma proteins, making its volume of distribution low. [35] Bempedoic acid possesses a half-life ranging from 15 hours to 24 hours. Regarding the drug clearance, bempedoic acid is primarily (about 70 percent) eliminated via the kidneys, and almost 30 percent is eliminated via the stool. [36]

Pleiotropic effects

Despite the liver-specific action of bempedoic acid and no muscle-related adverse effects, it has been proven that bempedoic acid exhibits anti-inflammatory effects. In addition, reduced TNF levels were found in human macrophages after being treated with 50-100μM of bempedoic acid. [37] Besides this, bempedoic acid is currently under many research investigations and clinical trials, and no clear data is available on the pleiotropic effects of bempedoic acid. Therefore, further research is required to obtain more information on them.

5. Non-Statin LDL Cholesterol/Triglyceride-Lowering & HDL Raising Therapy (Fibrates, Nicotinic acid)

Fibrates

Mechanism of action

Fibrates' mechanism of action occurs through various means such as promoting the uptake of fatty acids, catabolizing beta-oxidation pathways, decreasing triglyceride synthesis, and then converting to acyl CoA derivatives.38 Further, fibrates increase HDL and reverse cholesterol transport, which leads to an increase in apo-AI and apo-AII. [38,39] Fibrates act on a molecular level by inducing the activation of transcription factors of the peroxisome proliferator-activated receptor (PPAR). [39] PPAR-alpha controls

the transcription of the ApoC-III gene, which, when increased, can lead to hypertriglyceridemia. Conversely, a decrease in ApoC-III leads to the breakdown of VLDL and decreases triglyceride levels. [38,39] Fibrates may also raise HDL levels through a similar mechanism by binding to a peroxisome proliferator response element (PPRE), which increases the transcription and subsequent production of apo-AI.

Pharmacokinetics

Fibrates are primarily administered daily through an oral tablet formulation and are metabolized in the liver through the cytochrome p450 pathway, specifically CYP 3A4. Fibrates are then excreted renally; therefore, patients with renal complications should be given smaller doses and monitored closely as the drug will have an increased half-life. Further special precaution must be taken in patients who are on drugs or other substances which alter the CYP450 system for a possible altered metabolism. [40]

Pleiotropic effects

There are relatively few pleiotropic effects associated with fibrate usage as toxicity is not common. An increase in serum creatinine may be seen as a result of the PPAR-alpha mechanism. [41] ALT and AST levels may also show fluctuations due to fibrate usage. HMG Co-A reductase inhibitors, such as statins, are monitored, as fibrates may increase their half-life with a potential for rhabdomyolysis or myopathy; however, this risk is low. Currently, fenofibrate is used to treat high-risk patients on statins for atherogenic dyslipidemia. [42]

Nicotinic acid

Mechanism of action

Nicotinic acid, also known as Niacin (NA), is a water-soluble vitamin used to treat hyperlipidemia. [43] This drug works by reducing the levels of TGs, apolipoprotein-B containing lipoproteins, VLDL, LDL, and increasing HDL levels. [44] Niacin also lowers the plasma concentration of lipoprotein a [Lp(a)], linked to the pathophysiology of coronary heart disease. [45] This makes Niacin an excellent treatment option for a wide range of lipid disorders. The use of Niacin is also limited to side effects such as cutaneous flushing, skin rash, and stomach distress. [43]

Effect on VLDL, LDL and Triglycerides

Niacin lowers the levels of VLDL, LDL, and TG's by two main mechanisms, including:

(1) the suppression of TG lipolysis in adipose tissue, which leads to a lower transit of free fatty acids (FFAs) to the liver, reducing VLDL production rate, and

(2) the manipulation of liver TG synthesis and secretion of VLDL particles, which leads to enhanced breakdown of apo B intracellularly. [46,47]

Inhibition of lipolysis in adipose tissue might be one mechanism for lowering excessive lipid levels in the blood. This is because the adipose tissue serves as a primary source of free fatty acids and glycerol for the liver to produce VLDL, which is then released into circulation. [48] VLDL synthesis is stimulated by plasma glucose and metabolites, dietary cholesterol in plasma chylomicrons, and plasma-free fatty acids. The reduction in these substrates might explain nicotinic acid's therapeutic impact. [43] Niacin can also boost intracellular apo B breakdown and reduce VLDL and LDL particle production by decreasing hepatocyte diacylglycerol acyltransferase and triglyceride synthesis. [48]

Effect on HDL

High-density lipoproteins salvage free cholesterol from a variety of tissues and play an important role in eliminating cholesterol from peripheral cells and transferring it to the liver. [48] Nicotinic acid is thought to increase HDL levels by influencing its metabolism. Niacin raises HDL by lowering the fractional

catabolic rate of HDL-Apolipoprotein AI (Apo-AI) while leaving the synthetic rates unaffected. Furthermore, in individuals with low HDL, Niacin specifically raises plasma levels of Lp-AI, a cardioprotective subfraction of HDL. [48] In a meta-analysis to determine the efficacy and safety of the HDL-decreasing drugs (Niacin versus fibrates), results showed that Niacin increased the levels of HDL-C by 16%. [44]

Effect on Lp(a)

According to the Framingham study, lipoprotein(a) [Lp(a)] is an independent risk factor for coronary artery disease, with a two- to three-times increased risk. [49] Niacin has been shown to reduce Lp(a) levels. Extended-release nicotinic acid reduced Lp(a) plasma concentrations by 20%, synthesis rates by 50%, and catabolism by 37% in research to assess the effect of nicotinic acid on circulating Lp(a) concentrations in patients with elevated triglycerides. [50] Decreased apo(a) transcription or apoB secretion by suppression of TG synthesis are two possible ways by which Niacin decreases Lp(a). [46,51]

Pharmacokinetics

Nicotinic acid is virtually completely absorbed when given orally, and it reaches peak plasma levels in about an hour. The drug is absorbed more quickly in the small intestine than in the stomach. In the urine, around 88 percent of an oral dosage can be found as unaltered drugs or metabolites, indicating that gastrointestinal absorption is near total. [43]

Pleiotropic effects

Niacin has a variety of non-hypolipidemic effects, such as anti-oxidative, anti-inflammatory, and antithrombotic properties, all of which influence the development of atherosclerosis. It also has potential clinical indications for use in non-alcoholic fatty liver disease and chronic renal insufficiency. It increases adiponectin concentration and affects glomerular filtration. Niacin also reduces dietary phosphorus absorption in the GI tract. [52]

Anti-oxidative and Anti-inflammatory properties of Niacin:

Niacin has been shown to reduce oxidative stress and inflammation in the blood vessels, which helps to alleviate endothelial dysfunction. Research by Ganji et al. (2009) showed that Niacin boosted nicotinamide adenine dinucleotide phosphate (NADPH) levels by 54% while at the same time lowered endothelial reactive oxygen species (ROS) generation, LDL oxidation, and release of inflammatory cytokines. [53] In 54 participants with stable coronary artery disease, adding Niacin to their existing medication for three months resulted in lower levels of lipoprotein-associated phospholipase A2 and C-reactive protein. [54]

6. Non-Statin Triglyceride-Lowering Therapy (Volanesorsen)

Volanesorsen

Mechanism of action

The Volanesorsen has decreased ApoCIII levels, thereby inhibiting ApoCIII mRNA. Normally, ApoCIII inhibits LPL and hepatic lipase, causing the reduction in the hepatic uptake of triglyceride-rich lipoprotein (TRL) remnants. Volanesorsen stimulates the catabolism of TRLs by the LPL-independent pathway, blocks protein synthesis, and limits mRNA availability enhancing ribonuclease H1-mediated degradation. This leads to low levels of ApoCIII in the liver. [55]

Effects on clinical trials

A clinical trial involving familial chylomicronemia syndrome has shown a decrease of 77% in TG levels related to the change in Apo CIII. Additionally, there were fewer pancreatitis events with volanesorsen therapy.[56] Likewise, patients with multifactorial chylomicronemia exhibited lower

TG levels and acute pancreatitis. [57] Otherwise, studies have shown concerns about the correlation between volanesorsen and thrombocytopenia. [58]

7. Non-Statin LDL Cholesterol-Lowering & HDL Raising Therapy (PCSK9 Inhibitors)

PCSK9 Inhibitors (Evolocumab, Alirocumab)

Mechanism of action

PSCK9 is part of the family of proprotein convertases, which are enzymes that turn proproteins into their active protein forms. Its active form binds to the LDL-C cellular receptors on hepatic cells, signaling them for degradation. Hence, overall LDL-C receptor activity decreases, resulting in increased LDL-C. The latter happens because LDL-C needs to bind its receptors to get into the cells. If it doesn't, blood levels of LDL-C begin to rise. Since PCSK9 inhibitors block the action of PCSK9 proteins, more LDL-C receptors are expressed, which lowers the LDC-C. [58,59]

Alirocumab and Evolocumab are IgG1 and IgG2 monoclonal antibodies that inhibit the PCSK-9 enzyme and prevent reduction in LDL receptors, respectively. [60,61] Increase in LDL receptors on the hepatocyte surface leads to a decrease in LDL cholesterol levels.60 Alirocumab has significantly reduced LDL cholesterol in phase 3 clinical trials. In addition, the ODYSSEY OUTCOMES study has proven its long-term effectiveness. [62]

Pharmacokinetics

When administered subcutaneously, evolocumab bioavailability is 72% and 85% for a standard dose of alirocumab (75 mg every two weeks). Their half-lives are of approximately up to 20 days. Low doses of evolocumab (<140 mg) are eliminated through nonlinear pharmacokinetics by binding to its target PCSK9, while higher doses are eliminated by endogenous IgG clearance in cells of the

reticuloendothelial system. Due to its large weight, almost no renal excretion is expected. Low concentrations of alirocumab are eliminated mainly through saturable binding to the target (PCSK9), while higher concentrations are eliminated mainly through a nonsaturable proteolytic pathway. [63]

Pleiotropic effects

Besides increasing plasma LDL, PCSK9 appears to promote the initiation and progression of atherosclerosis. Hence, its inhibition lowers lipids but may slow atherosclerosis development and reduce overall cardiovascular risk. However, the exact molecular mechanisms behind this possibility are still uncertain. [64]

8. Non-Statin LDL Cholesterol & Triglyceride-Lowering Therapy (ANGPTL3 Inhibitors)

ANGPTL3 Inhibitors

The ANGPTL3 inhibitors play an essential part in lipid metabolism, modulation, and disorders. They are secreted by the liver and act to promote hypolipidemia. [65] ANGPTL3 binds to LPL and EL, releasing FFAs and phospholipids from VLDL and HDL-C. The inhibition of this protein interferes in the hydrolysis of TGs and phospholipids by inhibiting lipoprotein lipase (LPL)-mediated, and endothelial lipase (EL) mediated hydrolysis. [66] Inhibition of ANGPTL3 also results in decreasing levels of plasma TGs, apoB, LDL-C, and HDL-C. [67]

Evidence shows that low plasma levels of LDL-C can occur due to the loss of LDLR function or pharmacological inhibition. Meanwhile, the pharmacological pathway may be more interesting for the treatment of HoFH. [66] Scientists have also discovered that the LDLR modulation of ANGPTL3 inhibitors is not affected by cholesterol reduction. This indicates that ANGPTL3 could be used in patients with null LDLR mutation. [68] Although the mechanism is not fully clear yet, research shows that some hormones, like insulin, leptin, and thyroid, could act as ANGPTL3 inhibitors. [69] This inhibition leads to insulin sensitivity and reduction of diabetes risk. [65]

Moreover, loss of ANGPTL3 gene functioning may seem to lower CAD risk among patients, even with the reduction in HDL-C level. [66] Recently, researchers have proven that Evinacumab is a promising drug for refractory hypercholesterolemia treatment in patients with loss of LDLR function. It is an ANGPTL3-blocking monoclonal antibody approved by USA FDA and EMA for patients over 12 years with HoFH. [65]

9. Gene-based LDL Cholesterol-Lowering Therapy: Small interfering RNAs (Inclisiran, Olpasiran, Antisense oligonucleotides, Vupanorsen, Mipomersen, Volanesorsen, IONIS-ANGPTL3-Lrx)

Inclisiran

Inclisiran is a synthetic small interfering RNA (siRNA) molecule that exerts its therapeutic action to lower LDL levels and decrease cardiovascular events by targeting proprotein convertase subtilisin-kexin type 9 (PCSK9). [70] siRNA functions mainly to regulate gene expression. [71] By interacting intracellularly with the RNA-induced silencing complex (RISC), Inclisiran activates the natural mechanism of RNA interference (RNAi), allowing it to break messenger RNA (mRNA) molecules expressing PCSK9. The cleaved mRNA is destroyed and consequently is unable to undergo translation, resulting in lower PCSK9 protein levels. [72]

Inclisiran was approved in December 2021 by the Food and Drug Administration (FDA) as a two-dose a year therapy for LDL-C. The approval of this drug came after Inclisiran showed promising results in the Phase III ORION-9, ORION-10, and ORION-11 clinical trials.

ORION-9 was a double-blind, randomized phase 3 trial in which 482 adults with heterozygous familial hypercholesterolemia (FH) and elevated LDL-C were randomly assigned to receive either 300mg of Inclisiran sodium or placebo. Results showed that persons with heterozygous familial

hypercholesterolemia who got Inclisiran inconsistently had considerably lower LDL cholesterol levels, specifically 47.9%, compared to those who received a placebo. [73] ORION-10 and ORION-11 were double-blind, randomized phase 3 trials that evaluated the efficacy, safety, and adverse events of Inclisiran in patients with high cardiovascular risk disease who had elevated LDL cholesterol levels although receiving maximum statin therapy. Results showed that with Inclisiran injected twice a year, LDL cholesterol levels were reduced by nearly 50%. [74]

Inclisiran has its advantages compared to other drugs for hypercholesterolemia. Its infrequent dosing can improve patient compliance by administering subcutaneously once every three to six months. The drug has also been associated with minimal side effects, the most common being headache, mild rash, hyperpigmentation, musculoskeletal pain, back pain, hiccups, and acute nasopharyngitis. A disadvantage of this drug is that due to its long-lasting activity for six months, any potential long-term detrimental effects are difficult to reverse. [75]

Olpasiran

Lipoprotein (a) plays a causative role in cardiovascular disease based on compelling evidence. The discovery and development of olpasiran, a first-in-class synthetic, double-stranded, N-acetyl galactosamine-conjugated small interfering RNA (siRNA), may bring an end to the era in which there are no pharmacotherapies directly targeting Lp(a) available for clinical use. It was created to directly inhibit LPA messenger RNA synthesis in hepatocytes and significantly lower plasma Lp(a) levels. Olpasiran lowered Lp(a) concentrations in transgenic mice and cynomolgus monkeys in a dose-dependent manner, with up to an 80% drop from baseline following a single treatment for 5-8 weeks. The primary outcome of an olpasiran dose-escalation experiment was safety and tolerability, with Lp(a) concentrations and pharmacokinetic parameters as secondary outcomes. [76]

Antisense oligonucleotides

This powerful RNA targeting therapy utilizes short single-stranded nucleotides called antisense oligonucleotides (ASOs) that bind to their target mRNAs and lead to positive or negative changes in translation.

Vupanorsen/IONIS-ANGPL3-Lrx

Vupanorsen (AKCEA-ANGPTL3-L Rx) is an N-acetyl galactosamine-conjugated antisense oligonucleotide that inhibits angiopoietin-like 3 (ANGPTL3) protein synthesis, specifically in the liver. It improves lipid/lipoprotein profiles and may be used to reduce residual cardiovascular risk.[77] A major role of angiopoietin-like proteins 3 and 4 (ANGPTL3 and ANGPTL4) in regulating the activity of lipoprotein lipase (LPL). Antagonizing the hydrolysis of triglycerides has been discovered among the determinants of atherosclerotic cardiovascular disease (ASCVD) based on genetic and experimental evidence. Inactivation of ANGPTL3 employing monoclonal antibodies or antisense oligonucleotides significantly decreases plasma LDL-C and triglyceride levels, according to clinical investigations in individuals with various dyslipidemia.[78] Reduced levels of ANGPTL3 in the blood are also linked to decreased triglycerides and other atherogenic lipids, making it a promising target for Familial partial lipodystrophy (FPLD) treatment. Therefore, using vupanorsen to target ANGPTL3 may help people with FPLD with a variety of metabolic issues.[79]

Mipomersen

Mipomersen is an antisense oligonucleotide that inhibits apolipoprotein B synthesis, lowering VLDL and LDL levels. [80] It targets mRNA encoding ApoB apolipoprotein and prevents ApoB production. This, in turn, reduces hepatic production of different lipoproteins such as VLDL, LDL, and Lp(a). Mipomersen is an FDA-approved drug for treating homozygous familial hypercholesterolemia and is administered subcutaneously at 200 mg weekly. [81] It's only valuable for patients who haven't

responded to earlier treatments and are more effective than other drugs with more manageable side effects. [80]

Volanesorsen

Familial chylomicronemia syndrome is a rare hereditary condition characterized by chylomicronemia and recurrent pancreatitis due to decreased lipoprotein lipase activity. The drug volanesorsen was created to treat familial chylomicronemia syndrome (FCS), hypertriglyceridemia, and familial partial lipodystrophy (FPL). In 77 percent of patients with familial chylomicronemia syndrome, it reduced triglyceride levels to less than 750 mg per deciliter. [82]

Volanesorsen has also been identified as a possible diabetic dyslipidemia therapy. Apolipoprotein CIII (ApoCIII), a recognized inhibitor of lipoprotein lipase, appears to be involved in the mechanisms driving insulin resistance-induced diabetes dyslipidemia. In patients with T2DM, the quantity of very-low-density lipoprotein1 (VLDL1) with a greater TG content and abundant ApoCIII was shown to be considerably higher. [83]

10. Adeno-associated virus vectors: Triglyceride- Lowering Therapy (Alipogene tiparvovec, AAV8.TBG.hLDLR)

This mode of gene therapy is of great interest as it utilizes the help of a viral vector to deliver and incorporate DNA genes to treat the underlying disease. One of the most widely used viral vectors is adeno-associated viruses (AAVs) because of their efficient transfection and transduction capabilities. [84] The use of such AAVs is increasing day by day in hypercholesterolemia management, especially in the field of hypercholesterolemia management of familial cases.

Alipogene tiparvovec

Alipogene tiparvovec is an adeno-associated virus Type I (AAV1) gene therapy containing the LPL S447x gene. It uses recombinant baculovirus technology and insect cells to guarantee the increase in

transduction efficiency of the human LPL gene variant (LPLS447x) in skeletal muscle cells. It detects LPL activity, decreases TGs levels, and enhances lipoprotein turnover. [85,86] Studies have shown that the intramuscular injection of alipogene tiparvovec will cause persisting expression of the AAV1-LPLS447X genome in muscle cells. Then, there will be a decrease in TG levels and complete resolution of lipemia. Also, the LPL gene will be activated. [85,87] Although the AAV vector-mediated gene transfer was associated with local T cell-mediated immune responses to the AVV vector; it did not have clinical consequences for the patient. [85]

AAV8.TBG.hLDLR

AAV8.TBG.hLDLR is a recombinant AAV8 vector containing the human LDLR gene that has not yet been studied in humans. This vector aims to deliver functional LDLR genes to patients with a mutation in both LDLR alleles. [88] Promising studies showed that this gene vector therapy was only associated with mild histopathology in the liver and transaminases. [89] Also, researchers demonstrated that AAV8.TBG.hLDLR is a possible option in FH treatment. [90]

11. CRISPR/Cas9 based therapeutics

This fascinating molecular system enables gene editing and allows modification/repair of target genetic sequences directly using CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9. Thus, inactivating mutations in ApoC3, ApoB, PCSK9, etc., can be repaired via this gene therapy. The first positive results of this gene therapy were obtained when PCSK9 inhibition was done in mice with Streptococcus pyogenes Cas9 and guided RNA within the adenovirus vector. A significant reduction of 90 percent was observed in the PCSK9 level without any noticeable side effects. [91,92]

12. Non-coding RNA therapy (miRNAs, AAV8 vector-expressing LeXis therapy)

One of the most important regulators of central dogma includes the long non-coding RNAs (IncRNAs), mostly greater than 200 bp long. These non-protein oligonucleotides are essential in genetic regulation and genome expression. [93] Recent advances have been emerging in the study of IncRNAs for cholesterol homeostasis. Diverse functions of lncRNAs have been identified, including their role in developing several lipid disorders. Still, the exact function of such astonishing molecules is poorly known, and further studies are implicated for better understanding.

miRNAs

MicroRNAs or miRNAs are a highly conserved class of non-coding RNAs (approximately 18-22 nucleotides) abundantly present in eukaryotic organisms, including human cells. Of the various functions of MiRNAs, mRNA degradation, translation inhibition, and formation of silencing complexes are notable. Thus, dysregulated behavior of such miRNAs can result in disease development by altering genetic networks. [94]

Therapeutic inhibition of specific miRNAs can allow clinicians to alter the expression of genes so that certain disease processes are resolved. One approach that is commonly being applied these days for controlling lipid metabolism is antisense oligonucleotides (ASOs) targeted against miRNAs. Table 1 demonstrates the tabulated details of several potential hyperlipidemia anti-miRNA drugs currently in different phases of clinical studies. [95-97]

AAV8 vector-expressing LeXis therapy

In a research-based murine model clinical study, Peter Tontonoz et al. used AAV8 vector-expressing LeXis (lncRNA liver-expressed liver X receptor-induced sequence) to identify its therapeutic implication in familial hypercholesterolemia for reducing lipid levels. Under the control of liver-specific TBG

(thyroxine-binding globulin) promoter, this AAV (adeno-associated virus) therapy caused sustained expression of LeXis with a concomitant reduction of Srebp2. Significantly reduced lipids were found in the livers of animal models via histological analysis. A significant decrease in total cholesterol and triglyceride levels in the serum was also found. Thus, AAV8 vector-expressing LeXis can be a potential therapeutic intervention in cholesterol diseases like atherosclerosis. [98]

13. Therapeutic lncRNAs Targeting (MIAT, lncARSR)

MIAT

MIAT (myocardial infarction-associated transcript) is a lncRNA that acts as a hypoxia-response gene. In a study, MIAT was markedly increased in patients with atherosclerosis. [99] Until now, it has been found that MIAT increases blood lipid levels, increases the lipid content of the atherosclerotic plaque, and decreases the collagen content of atherosclerotic plaque. [100] Thus, MIAT could be a potential target for the treatment of atherosclerosis.

lncARSR

lncARSR is an Akt signaling regulator located in chromosomal regions of 9q21.3. [101] Its expression was found profoundly increased in hypercholesterolemia patients and mice fed with high-cholesterol food. Inhibition of lncARSR in high-cholesterol-fed mice caused a striking reduction in serum lipid level compared to control mice. [102] This implied that lncARSR could serve as a potential target for cholesterol diseases.

14. Conclusion:

Statins have been the mainstay of lipid-lowering therapy over the years, and it is undeniable their contribution to the primary prevention of cardiovascular disease and the lowering of lipids. Despite their proven efficiency, many patients do not often achieve adequate LDL-C or triglyceride-rich lipoprotein

(TRL) reduction. However, studies have shown that non-Statin therapies are promising in treating patients that do not benefit from statin therapy. Most of these drugs can result in lower LDC-C plasma levels, TRL hepatic uptake, TG levels, VLDL levels, and HDL levels. In addition, the adeno-associated virus vectors will benefit the patients in hypercholesterolemia management and FH treatment. Another promising alternative to statins is gene-based therapy, which interferes with RNA molecules to decrease LDL levels and reduce cardiovascular events. They act to affect the ANGPTL3, ANGPTL4, and PCSK9 proteins. Lastly, researchers have shown encouraging results in IncRNAs targeting, non-coding RNA, and CRISPR/Cas9 based therapeutics.

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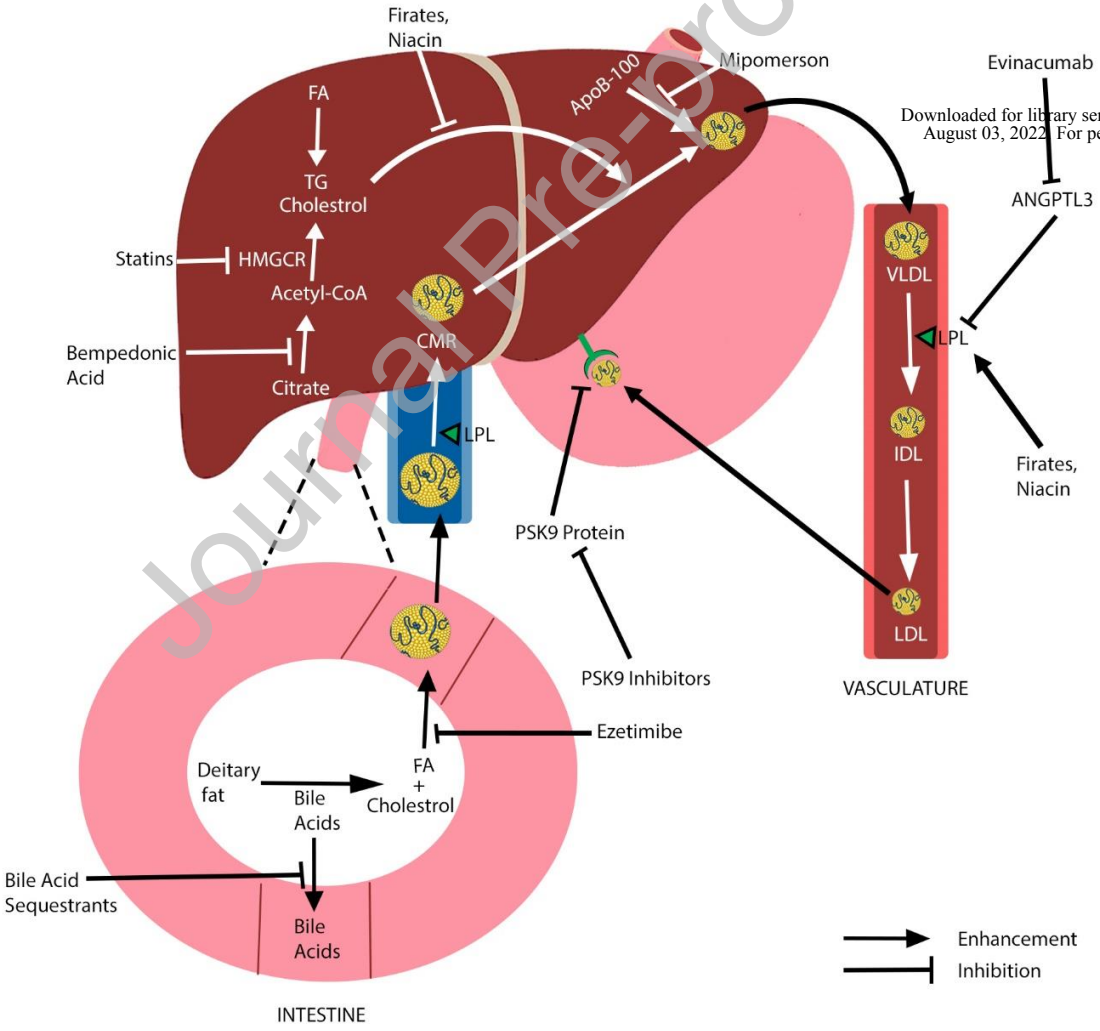

Figure 1. A Diagrammatic illustration of Lipid Metabolism with Sites and Targets of Lipid Lowering Drugs

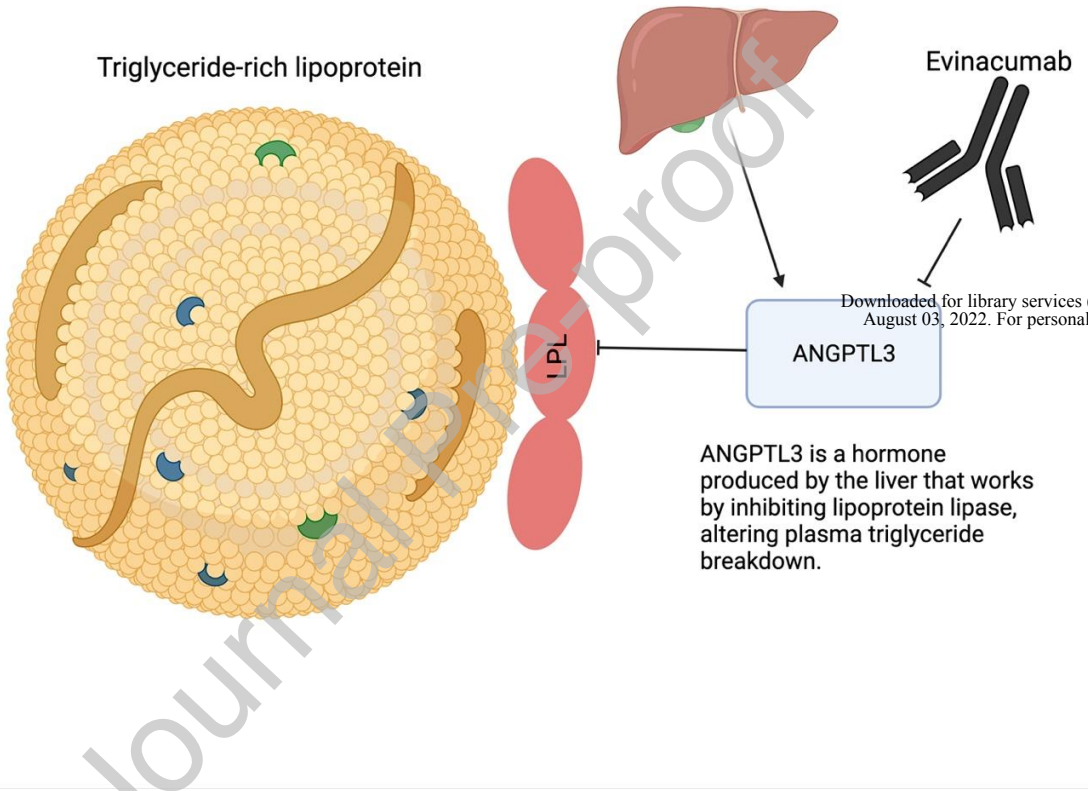

Figure 2. Mechanism of Action of ANGPTL3 Inhibitors

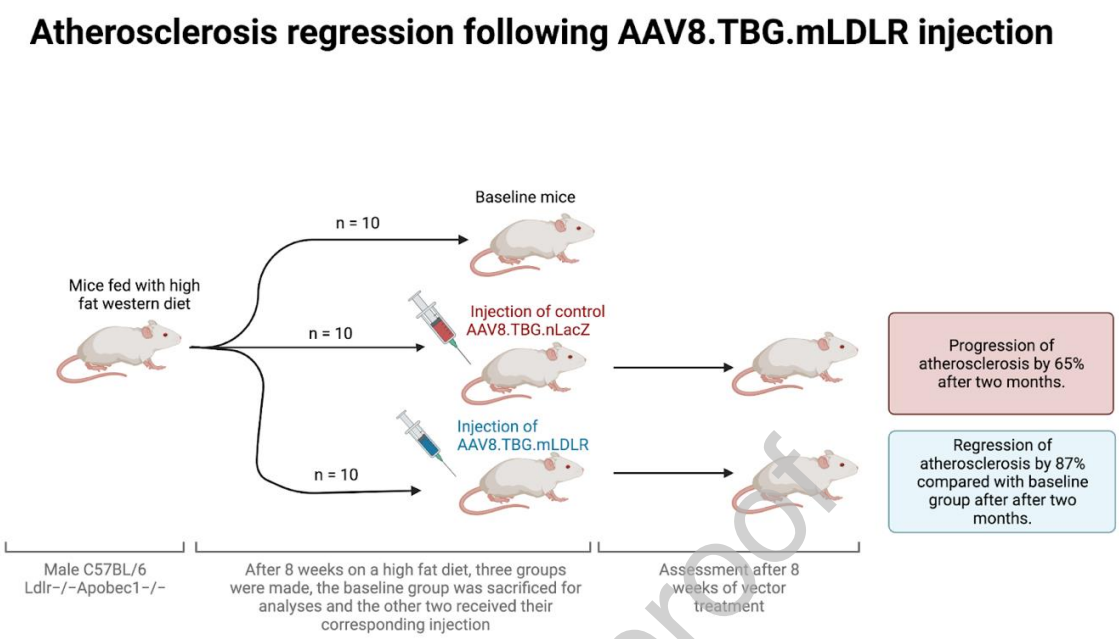

Figure 3. A Schematic Illustration of Atherosclerosis Following AAV8. mLDLR injection

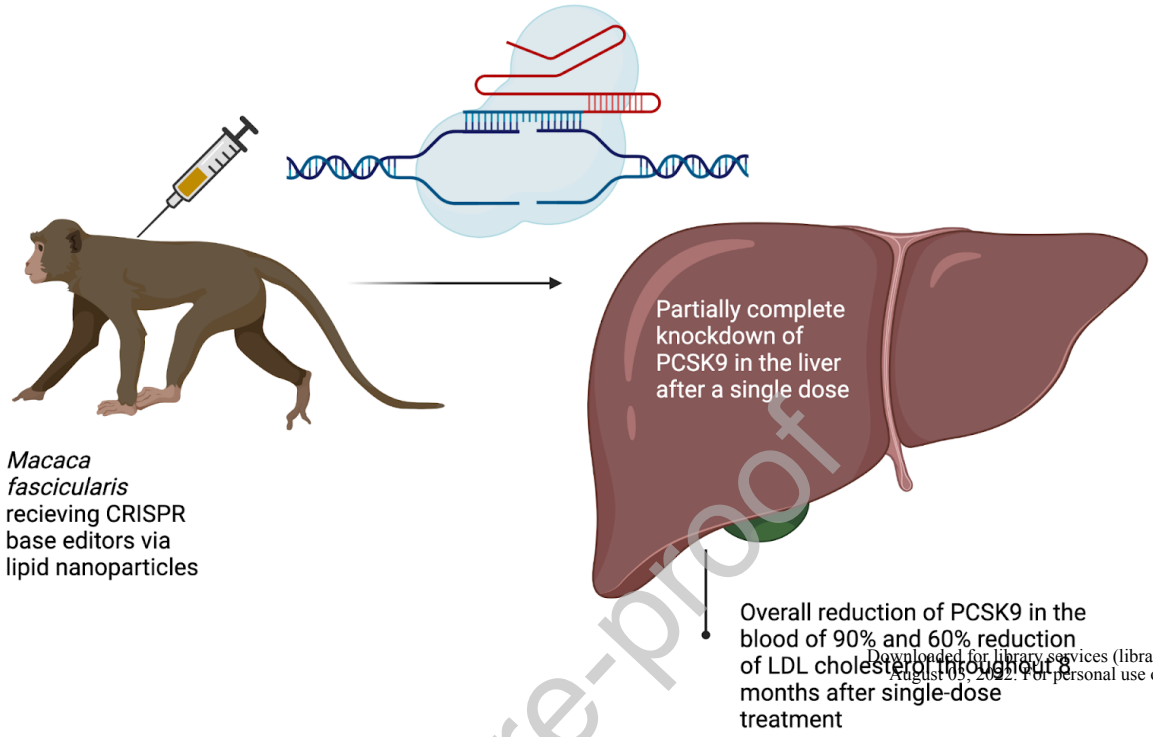

Figure 4. Application of CRSPR Technology in Lipid Lowering Therapy

Developmental Drug	**Targeted MiRNA**	**Indicated Disease**	**Targeted Tissue**

MGN-9103[95]	MiR-208	Metabolic syndrome, diabetes mellitus, obesity	Heart
Miravirsen[96]	MiR-122	Hepatitis C, hyperlipidemia	Liver
MGN-1374[97]	MIR-15 family	Myocardial Infarction	Heart

Table 1: Tabulated details of several potential hyperlipidemia anti-miRNA drugs currently in different phases of clinical studies.

Drug name	**Specific drug examples**	**Mechanism of Action**	**Indications for use**	**Efficacy Proven on Previous studies**	**Pleiotropic effects**	**Side effects and cautions**

Statins	Atorvastatin Rosuvastatin	Competitively inhibit HMG-CoA reductase	Primary prevention of cardiovascular disease.	One early study examined a dose-dependent reduction of LDL cholesterol - ranging from 25 to 60% - following atorvastatin therapy.[7]	Increased inflammatory response, enhance stability of atherosclerotic plaques, improving endothelial functioning, inhibit clotting	Myalgia, rhabdomyolysis, thrombocytopoenia, gastrointestinal upset
Bile acid sequestrants	Cholestyramine	Strongly positively charged molecules that adhere to negatively charged bile acids in the stomach, diminishing their lipid solubilizing activity and, as a result, limiting cholesterol absorption.	Bile acid agents are usually reserved for those patients who do not respond to dietary modifications or exercise therapy first, however, they may be used in conjunction with the therapy as well.[12] They have also been beneficial as second line agents for patients experiencing cholestatic disease	In the Lipid Research Clinics Coronary Primary Prevention Trial, it was proven to cut LDL cholesterol levels by 12.6 percent when compared to placebo. When compared to the control group, cholestyramine treatment resulted in a 19% reduction in the combined end outcome.[24]	Pleiotropic effects include improving non-cholesterol lipid metabolism, improving glucose metabolism, as well as energy metabolism, anti-inflammatory and anti-thrombotic effects.[29]	Hyperchloremic acidosis, asthma-like symptoms and increase in serum transaminases and alkaline phosphatase.[1][2]

	Colestipol		pruritis.	patients with typical phenotypes of hyperlipidemia who were given 5 gm of colestipol hydrochloride three times daily achieved an average reduction in cholesterol levels of 40 mg/100 ml (14%).[25]		Edema, syncope, dizziness, drowsiness, headaches, neuralgia, parenthesia, skin rashes, irritation, weight gain or loss, abdominal pain, biliary colic, constipation, dental discoloration, diarrhea, steatorrhea, abnormal hepatic function teste, anemia, adenopathy, dyspnea, and wheezing. Also, angina, chest pain, tachycardia, musculoskeletal pain, oint pains, aches or pain in the extremities, arthritis, backache, anorexia, weakness, fatigue, and swelling of the hands or feet. [103]

	Colesevelam			Lowering mean LDL cholesterol levels by up to 18%, and well tolerated with no significant side effects.[26]		Gastrointestinal obstuction, decrease in oral contraceptives efficacy and vitamin K deficiencies.[103]
Fibrates	Fenofibrate	Occurs through various means such as promoting the uptake of fatty acids, catabolizing beta oxidation pathways, decreasing triglyceride synthesis, and then converting to acyl coA derivatives. Further, fibrates increase HDL and reverse cholesterol transport, allowing for the increase in apo-AI and apo-AII.[38,39]	Small doses to patients with renal complications. Pay attention when patients are on drugs which alter CYP450, It can alter the metabolism of fibrates.	In one study aiming to study the effects of fibrates on lipid profile of diabetic patients, it was found that fibrates caused a decrease in total cholesterol by 1.15 ± 2.24 mmol/l and in triglycerides by 1.73 ± 2.96 mmol/l.[104]	An increase in serum creatinine may be seen as a result of the PPAR-alpha mechanism.[41] ALT and AST levels may also show fluctuations as a result of fibrate usage.	Fibrates are then excreted renally, therefore, patients with renal complications should be given smaller doses as the drug will have an increased half-life.[40] Patients with renal complications should be monitored closely. Further special precaution must be taken in patients who are on drugs or other substances which alter the CYP450 system as a major potential for

						altered metabolism is present.

Nicotinic acid	Niacin	Water-soluble vitamin used in the treatment of hyperlipidemia.[43] The drug works by reducing the levels of triglycerides (TG) and apolipoprotein-B containing lipoproteins very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL) levels.[44] Niacin also lowers the plasma concentration of lipoprotein a [Lp(a)], which has been linked to the pathophysiology of coronary heart disease.[45]	Wide range of lipid disorders	Extended-release nicotinic acid reduced Lp(a) plasma concentrations by 20%, synthesis rates by 50%, and catabolism by 37% in a research to assess the effect of nicotinic acid on circulating Lp(a) concentrations in patients with elevated triglycerides.[50]	Niacin has a variety of non-hypolipidemic effects, such as anti-oxidative, anti-inflammatory, and antithrombotic properties, all of which influence the development of atherosclerosis. It also has potential clinical indications for use in non-alcoholic fatty liver disease and chronic renal insufficiency.[52]	Cutaneous flushing, skin rash, and stomach distress.[43]

Ezetimibe		Ezetimibe binds NPC1L1 (Niemann-Pick C1-like 1), which inhibits the intestinal absorption of biliary and dietary cholesterol. In turn, cholesterol stays in the lumen of the small intestine and keeps going further to be excreted.[31]	Hypercholesterolaemia that is not controlled on statins.	IMPROVE-IT study found that ezetimibe 10 mg/simvastatin 40 mg is more effective than simvastatin 40 mg monotherapy in preventing CV events in individuals who have had a high-risk ACS.[105]	Doubtful clinical relevance.	The common side effects include asthenia; diarrhoea; gastrointestinal discomfort; gastrointestinal disorders.
Bempedoic Acid		Inhibiting cholesterol biosynthesis metabolic pathway in the same manner as a statin. activated bempedoic acid (coenzyme A form) functions to inhibit ATP-citrate lyase within the hepatocytes.	It does not target muscle tissue, thus becomes an alternative for patients with statin-induced myopathy.[35]	In one meta-analysis, it was proved that bempedoic acid caused significant reduction in LDL, total cholesterol, non-HDL cholesterol, apolipoprotein B, and hs-CRP levels as compared to control subjects.[106]	It has been shown that bempedoic acid exhibits anti-inflammatory effects and reducing LTFs.	Upper Respiratory Tract Infections, Gout, Hyperuricemia, Decreased serum glucose levels, Liver dysfunction.[36]

Volanesorsen		The Volanesorsen has been shown to decrease APOCIII levels thereby inhibiting ApoCIII mRNA. The ApoCIII inhibits the interrupts LPL and hepatic lipase causing reducing the hepatic uptake of triglyceride-rich lipoprotein (TRL) remnants.	Adult patients with confirmed familial chylomicronemia syndrome (FCS) with a high risk of pancreatitis who have had an insufficient response to diet and triglyceride-lowering therapy.[56]	A clinical trial involving familial chylomicronemia syndrome has shown a decrease of 77% in TG levels related to the change in ApoCIII.[56]	Patients with multifactorial chylomicronemia showed lower TG levels and acute pancreatitis.	Studies have shown concerns about the correlation between volanesorsen and thrombocytopenia. [58]

PCSK 9 Inhibitors	**Evilocumab**	Its active form binds to the LDL-C cellular receptors on hepatic cells, signaling them for degradation. Hence, overall LDL-C receptor activity decreases, resulting in increased LDL-C. The latter happens because LDL-C needs to bind its receptors to get into the cells. If it can't, then blood levels of LDL-C will begin to rise. Since PCSK9 inhibitors block its function, there will be more LDL-C receptors available, which will lower the LDC-C.[59,61] Evolocumab is an IgG2 monoclonal antibody that inhibits the PCSK-9	The recommended dose is 15 mg/kg given intravenously over 60 minutes every 4 weeks.	The odyssey outcomes study has proven its long-term effectiveness. It has a 72% of bioavailability. Three clinical trials have proved that Evinacumab reduce LDL cholesterol level.	It inhibit the atherosclerosis initiation and progression. Also, It reduce lipids and overall cardiovascular risk.	It can cause mild local injection reactions, rhinorrhea, nasopharyngitis, dizziness, nausea, fatigue, and pain in the extremities.

		enzyme.[61]				

	Alirocumab	Alirocumab is an IgG1 monoclonal antibody that inhibits PCSK-9. Alirocumab inhibits the activity of the PCSK-9 enzyme and prevents the reduction of the number of LDL receptors. The increase in LDL receptors on the hepatocyte surface leads to a decrease in LDL cholesterol level.[60]	Primary Hyperlipidemia disorders, CVS adverse events prevention, homozygous familial hypercholesterolemia.	It has been observed to significantly reduce LDL cholesterol in phase 3 clinical trials.[62]	PCSK9 appears to promote the initiation and progression of atherosclerosis. Hence, its inhibition lowers lipids but may slow atherosclerosis development and reduce overall cardiovascular risk. Anti-atherosclerotic effects causing stabilization of atherosclerotic plaque, anti-coagluation effects, anti-platelet effects, lipid lowering effects causing slowing of bacterial infections and prevention of malarial infection, antineoplastic effects.[107]	Naospharyngeal infections, allergic reactions, UTIs, diarrhea, post-administration influenza infection, muscle spasms and myalgias, sinusitis, bronchitis.[108]

AGPL3 Inhibitors	**Evinacumab**	It is a monoclonal antibody that targets angiopoietin-like protein 3 (ANGPTL3) to decrease several lipid levels (predominantly LDL-cholesterol) in the serum of the patient.[109]	Used as adjunctive treatment for Homozygous Familial Hypercholesterolemia.	In a placebo-controlled phase III study, therapeutic efficacy of evinacumab was assessed in 65 patients of homozygous familial hypeercholesterolemia with significant improvement in lipid profile seen after 24 weeks.[110]	Evinacumab can be combined with statins for hypertriglyceridemia treatment in patients with familial hypercholesterolemia.[111]	Animal studies on rabbits have shown fetal-embryonic toxicity causing malformations at doses lower than those administered in humans. Also, overdosage can cause significant infusion reactions and/or dizziness, yet there is not enough supportive data for side effect profile of this drug.

Gene-based Therapy	**Inclisiran**	Inclisiran is a synthetic small interfering RNA (siRNA) molecule that exerts its therapeutic action to lower LDL levels and decreasing cardiovascular events by targeting proprotein convertase subtilisin-kexin type 9 (PCSK9).[70]	For those with ASCVD or heterozygous familial hypercholesterolemia (HeFH) who require additional LDL-C lowering besides with diet and maximal statin therapy.	ORION-9 was a double-blind, randomized phase 3 trial in which 482 adults with heterozygous familial hypercholesterolemia (FH) and elevated LDL-C were randomly assigned to receive either 300mg of inclisiran sodium or placebo. Results showed that persons with heterozygous familial hypercholesterolemia who got inclisiran inconsistently had considerably lower levels of LDL cholesterol, specifically 47.9 percent compared to those who received placebo.[73]	One study found that PCSK9 inhibitors, including inclisiran, may slightly decrease factor VIII levels and can contribute in preventing cardiovascular diseases.[112]	The drug has also been associated with minimal side effects, the most common being headache, mild rash, hyperpigmentation, musculoskeletal pain, back pain, hiccups and acute nasopharyngitis. A disadvantage of the drug is that due to inclisiran's activity lasting for six months, any potential long-term detrimental effects are difficult to reverse.[75]

	Olpasiran	First-in-class synthetic, double-stranded, N-acetylgalactosamine-conjugated small interfering RNA (siRNA). created with the goal of inhibiting LPA messenger RNA synthesis directly in hepatocytes and lowering plasma Lp(a) levels significantly.	It is administered subcutaneously.	Olpasiran lowered Lp(a) concentrations in transgenic mice and cynomolgus monkeys in a dose-dependent manner, with up to an 80% drop from baseline following a single treatment for 5-8 weeks.	No Pleiotropic effects have been noted at this time	No imminent side effects were noted in trials.[113] Studies are currently ongoing.

Antisense oligonucleotides	**Miipomersen**	This powerful RNA targeting therapy utilizes short single-stranded nucleotides called antisense oligonucleotides (ASOs) that bind to their target mRNAs and lead to positive or negative changes in translation. This novel drug targets mRNA encoding ApoB apolipoprotein and prevents ApoB production. This, in turn, reduces hepatic production of different lipoproteins such as VLDL, LDL and Lp(a). Ultimately, LDL-C decreases in a dose-dependent way.	Mipomersen is an FDA-approved drug for the treatment of homozygous familial hypercholesterolemia. It is administered 200 mg subcutaneously every week.	In one meta-analysis by Astaneh et al., mipomersen was found to significantly reduce LDL-C levels in familial hypercholesterolemia patients as compared to the placebo (mean difference: -24.79, 95% C.I (-30.15, -19.43), p value < 0.00001)[114]	Elevation in liver fat content as well as transaminase levels, which stabilized after treatment cessation.[115]	Injection site reactions, flu like symptoms. Monitor transaminase levels closely.[115]

	Vupanorsen	Vupanorsen (AKCEA-ANGPTL3-LRx) is a N-acetyl galactosamine-conjugated antisense oligonucleotide that inhibits angiopoietin-like 3 (ANGPTL3) protein synthesis specifically in the liver.	Vupanorsen improves lipid/lipoprotein profiles and may be used to reduce residual cardiovascular risk.	Clinical trials shows that vupanorsen lowed ANGPTL3 levels in a dose-dependent manner by 69.9% to 95.2%.[116]	Vupanorsen causes reduction in adipose tissue insulin resistance.[79]	It can address several metabolic abnormalities in patients with Familial partial lipodystrophy.[79]
	Volanesorsen	Second generation chimeric antisense oligonucleotide that selectively binds to apoC-III mRNA, this binding prevents the translation of the apoC-III mRNA, promoting triglyceride clearance and the overall lowering of plasma triglyceride levels via LPL-independent pathways.[56]	Created to treat familial chylomicronemia syndrome (FCS), hypertriglyceridemia, and familial partial lipodystrophy (FPL). Volanesorsen has also been identified as a possible diabetic dyslipidemia therapy.	In 77 percent of patients with familial chylomicronemia syndrome, it reduced triglyceride levels to less than 750 mg per deciliter.[82]	Volanesorsen has been reported to increase insulin sensitivity and reduce HbA1c by 3.4 mmol/mol (0.44%) in patients with moderate glycemic control (HbA1c>7.5 % (58mmol/mol)) and hypertriglyceridemia (200–500mg/dl; 2.26–5.65mmol/L). Overall reduction in	Volanesorsen has been associated primarily with injection site reactions and thrombocytopenia. Fatigue, headache, nausea and myalgias have also been reported. [82]

					apoC-III seems to correlate directly with increased insulin sensitivity.[56]	

Adeno-associated virus vectors	**Alipogene tiparvovec**	Alipogene tiparvovec is an adeno-associated virus Type I (AAV1) gene therapy containing the LPL S447x gen. It uses recombinant baculovirus technology and insect cells to guarantee the increase in transduction efficiency of the human LPL gene variant (LPLS447x) in skeletal muscle cells. It detects LPL activity, decreases TGs levels, and enhances lipoprotein turnover.[85,86]	The use of such AAVs is increasing day by day in hypercholesterolemia management, especially in the field of hypercholesterolemia management of familial cases.	In a 2-year open-label trial, Alipogene tiparvovec was well-tolerated in 14 lipoprotein lipase deficient patients and 7 of the patients showed ≥40% reduction in triglyceride levels between 3 and 12 weeks.[117]	No such pleiotropic effects have been found so far.	It is very well tolerated with only a few patients demonstrating localized, mild to moderate injection-site reactions. Also, the most commonly reported adverse effect is pain in the lower extremity.[85]

	AAV8.TBG. hLDLR	AAV8.TBG. hLDLR is a recombinant AAV8 vector containing the human LDLR gene that has not yet been studied in humans. The purpose of this vector is to deliver functional LDLR genes to patients with a mutation in both LDLR alleles.[88]		No sufficient data found	No sufficient data found	No sufficient data found

CRISPR/Cas 9 based therapeutics		This fascinating molecular system enables gene editing and allows modification/ repair of target genetic sequences directly using CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 . Thus, inactivating mutations in ApoC3, ApoB, PCSK9, etc. that can be repaired via the utilization of this gene therapy.[91]	No sufficient data found	The very first positive results of this gene therapy were obtained when PCSK9 inhibition was done in mice with Streptococcus pyogenes Cas9 and guided RNA within the adenovirus vector. A significant reduction by 90 percent was observed in the PCSK9 level without any noticeable side effects.[91]	No sufficient data found	No sufficient data found

Non-coding RNA therapy	**miRNAs**	Recent advances have been emerging in the study of lncRNAs (non-coding RNA) for cholesterol homeostasis. Of the various functions of MiRNAs, mRNA degradation, translation inhibition, and formation of silencing complexes are notable. Thus, dysregulated behavior of such miRNAs can result in disease development by altering genetic networks	The indication changes according to the target MiRNA: 1. MIR-208: indicated to patients with metabolic syndrome, diabetes mellitus, obesity.[95] 2. MiR-122: indicated to patients with Hepatitis C, hyperlipidemia.[96] 3. MiR-15 family: indicated to patients with myocardial infarction.[97]	Researches show significant reduction in atherosclerotic plaque size in mice treated with miR-33 ASOs.[118]	Studies have shown desregulation of miRNAs in cancer cells, allteres expression of miRNAs in immune cells, CAEs and CAFs, affecting tumor progression.[119]	It may have antidepressant side effects and nauseas.[119]

	AAV8 vector-expressing LeXis therapy	LeXis is robustly induced by Western diet or pharmacologic LXR activation and gates the promoter binding of RALY, a transcriptional coactivator for cholesterol biosynthetic genes in mouse liver.[98]	AAV8 vector-expressing LeXis can be a potential therapeutic intervention in cholesterol diseases like atherosclerosis.[100]	Significantly reduced lipids were found in livers of animal models via histological analysis. A significant decrease in total cholesterol and triglyceride levels of the serum was also found.	Clinical trials have shown that it may contribute to long term fatty liver development and hepatotoxicity. And, it may modify cardiometabolic phenotypes in large animal models.[98]	No sufficient data found
Therapeutic lncRNAs Targeting	**MIAT**	MIAT (myocardial infarction-associated transcript) is a lncRNA that acts as a hypoxia-response gene. In a study, MIAT was found to be markedly increased in patients with atherosclerosis.	Patients with atherosclerosis[99]. And, It is a specific biomaker of Chagas disease cardiomyopathy [120]	The efficacy of these drugs are unknown in consequence of the lack of data on clinical trial.[121]	It involves alteration in myocardial infarction, diabetic retinopathy, paranoid schizophrenia, microvascular dysfunction and formation of nuclear bodies, and neurogenic commitment.[122]	The side effects of gene therapy targeting lncRNAs drugs concern scientists due to the lack of basic research on the function of theses drugs.[121]

	lncARSR	lncARSR is an Akt signaling regulator located in chromosomal regions of 9q21.31.[101] Its expression was found profoundly increased in hypercholesterolemia patients and mice fed with high-cholesterol food. Inhibition of lncARSR in high-cholesterol-fed mice caused a striking reduction in serum lipid level as compared to control mice.	Patients with hypercholesterolemia.	The efficacy of these drugs are unknown in consequence of the lack of data on clinical trial.[121]	It contributes to the hepatic steatosis in non-alcoholic fatty liver disease and steatohepatitis. Researches also shows that lncARSR plays a oncogenic role in initiation and progression of NSCLC and may serve as a therapeutic pathway.	The side effects of gene therapy targeting lncRNAs drugs concern scientists due to the lack of basic research on the function of theses drugs.[121]

Table 2: Summary of Lipid Lowering Therapy