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REVIEW ARTICLE

Molecular Therapeutics in Development to Treat Hyperlipoproteinemia

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Abstract
Clinical endpoints caused by hyperlipoproteinemia include atherosclerotic cardiovascular disease and acute pancreatitis. Emerging lipid-lowering therapies targeting proprotein convertase subtilisin/kexin 9 (PCSK9), lipoprotein(a), apolipoprotein C-III, and angiopoietin-like protein 3 represent promising advances in the management of patients with hyperlipoproteinemia. These therapies offer novel approaches for lowering pathogenic lipid and lipoprotein species, particularly in patients with serious perturbations who are not adequately controlled with conventional treatments or who are unable to tolerate them. Molecular targets for these novel therapeutic agents were identified and validated through genetic epidemiology studies. Proprotein convertase subtilisin/kexin 9 inhibitors (e.g., monoclonal antibodies and small interfering RNA) have revolutionized hypercholesterolemia management by significantly reducing both low-density lipoprotein cholesterol levels and major cardiovascular events. Genome editing of *PCSK9* promises to provide a potential cure for patients with familial hypercholesterolemia. Several investigational lipoprotein(a)-targeting therapies aim to reduce the risk of atherosclerotic cardiovascular disease and aortic valve disease, although definitive clinical endpoint studies remain to be completed. Inhibition of *APOC3* messenger RNA expression by olezarsen and plozasiran significantly lowers plasma triglyceride levels and markedly reduces pancreatitis risk in patients with familial chylomicronemia syndrome. Finally, angiopoietin-like protein 3 inhibition by the monoclonal antibody evinacumab has transformed management of patients with homozygous familial hypercholesterolemia. Together, these novel agents expand the therapeutic cache, offering personalized lipid-lowering strategies for high-risk patients with hyperlipoproteinemia, improving clinical outcomes and addressing previously unmet medical needs.

1 Introduction

Hyperlipoproteinemia, a general term for elevated plasma levels of various lipoprotein species, is a significant risk factor for several clinical endpoints, including atherosclerotic cardiovascular disease (ASCVD), aortic valve disease, and acute pancreatitis [1]. Reducing plasma levels of atherogenic lipoprotein species such as low-density lipoprotein (LDL) with traditional medications, particularly statins and ezetimibe, has been shown to reduce clinical cardiovascular events and extend life [2]. However, some patients cannot tolerate statins and in those with severe genetic dyslipidemias, desirable LDL-cholesterol (LDL-C) levels are often not achievable. Thus, new therapeutic alternatives are needed. Furthermore, a related hyperlipoproteinemia, namely elevated lipoprotein(a) (Lp[a]), is associated with an increased risk of ASCVD and aortic valve disease, but this dyslipidemia cannot be effectively managed with existing therapies [3, 4]. In addition, patients with severe hypertriglyceridemia (HTG) are at a high risk of acute pancreatitis [5], while those with mild-to-moderate HTG have an increased ASCVD risk [6], but traditional therapies including statins and fibrates show minimal evidence of clinical benefit.

Recent advances in molecular therapeutics have introduced innovative treatment options that can precisely target key proteins that act in specific pathways involved in lipid metabolism. This review focuses on four therapeutic approaches that are currently under investigation or already in clinical use for hyperlipoproteinemia. These therapies target: (1) proprotein convertase subtilisin/kexin type 9 (PCSK9); (2) Lp[a]; (3) apolipoprotein (apo) C-III; and (4) angiopoietin-like 3 protein (ANGPTL3). Although we restrict our focus to these targets, we recognize that other targets such as cholesteryl ester transfer protein, microsomal triglyceride transfer protein, and ATP citrate lyase are being targeted using oral small molecules; such therapies will not be discussed here as

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Key Points

Hyperlipoproteinemias are disorders characterized by elevated levels of such species as low-density lipoprotein, lipoprotein(a), and triglyceride-rich lipoproteins, which include chylomicrons and very-low-density lipoproteins. Specific hyperlipoproteinemias are associated with a range of clinical endpoints, including atherosclerotic cardiovascular disease, aortic valve disease, and pancreatitis.

Traditional lipid-lowering medications, such as statins, while effective in many patients, are insufficient in some patients with genetic hyperlipoproteinemias and in those who develop intolerance. Therefore, the field of lipidology has been actively pursuing the development of newer, targeted, more effective, and better-tolerated therapies.

Genetic epidemiology has implicated molecular targets including proprotein convertase subtilisin/kexin 9, lipoprotein(a), apolipoprotein C-III, and angiopoietin-like protein 3 as being potentially effective for reducing pathogenic lipoprotein species and preventing adverse clinical outcomes.

New agents designed to inhibit these targets include monoclonal antibodies, adnectins, antisense oligonucleotides, small interfering ribonucleic acids, and genome editing platforms. Some have already been approved for clinical use, while others are in development with the expectation of approval within the next few years.

they are not strictly molecular or biological, but they are discussed elsewhere [1].

Proprotein convertase subtilisin/kexin type 9 inhibitors such as the monoclonal antibodies evolocumab and alirocumab and the small (or short) interfering ribonucleic acid (siRNA) inclisiran have revolutionized the management of hypercholesterolemia because of their potent ability to lower LDL-C levels and reduce cardiovascular events [7]. Meanwhile, emerging Lp(a) targeting therapies, including pelacarsen, olpasiran, muvalaplin, and zerlasiran, offer hope for individuals with elevated Lp(a) levels who are at increased risk for ASCVD and aortic valve disease [4, 5]. Anti-apo C-III therapies, such as the RNA suppressing agents volanesorsen, olezarsen, and plozasiran, have demonstrated substantial reductions in plasma triglyceride (TG) levels together with a reduced risk of pancreatitis in patients with severe HTG [8]. Finally, anti-ANGPTL3 therapies such as the monoclonal antibody evinacumab target multiple lipid pathways, providing another promising avenue for patients with refractory dyslipidemia [9], particularly those with homozygous familial hypercholesterolemia (HoFH) [10]. This review aims to synthesize the current evidence on these molecular therapeutics, highlighting their mechanisms of action, clinical efficacy, and potential role in the current and future management of hyperlipoproteinemia.

2 Anti-PCSK9 Therapies

The discovery of PCSK9 has radically transformed dyslipidemia therapeutics [11]. Ubiquitously expressed, PCSK9 binds to and degrades LDL receptors [12]. This action is most relevant in the liver. Hepatic LDL receptors bind to apo B-100, a large protein found on the surface of atherogenic lipoproteins, thus facilitating their clearance from plasma via receptor-mediated endocytosis [12]. The most abundant apo B-100-bearing lipoprotein is the LDL particle. When PCSK9 binds to LDL receptors extracellularly and promotes their degradation intracellularly, there is decreased clearance of LDL particles from the plasma. Conversely, inhibition of PCSK9 results in increased clearance of LDL [12].

The relationship between PCSK9 and LDL-C was first described more than 20 years ago. In 2003, a genetic study identified gain-of-function mutations in the *PCSK9* gene that caused autosomal dominant hypercholesterolemia [13]. Subsequently, subgroup analyses of the Dallas Heart Study found that individuals who carried one copy of two different types of loss-of- function alleles of *PCSK9* had reduced LDL-C levels [14] and also that such naturally occurring variants were associated with an ~80% lifetime reduction in coronary heart disease events [15]. These genetic studies inspired the idea that pharmacologic inhibition of PCSK9 could reduce LDL-C and prevent ASCVD endpoints. Table 1 provides a summary of PCSK9 inhibitors, both approved and under investigation.

2.1 Monoclonal Antibodies Against PCSK9

In 2015, the US Food and Drug Administration (FDA) and many other regulatory agencies approved two PCSK9 monoclonal antibodies, evolocumab (Repatha®) and alirocumab (Praluent®). These agents are fully human monoclonal antibodies that bind circulating PCSK9, directing it to the reticuloendothelial system for elimination. Depletion of PCSK9 allows for greater intracellular recycling of LDL receptors as their degradation is reduced. This increases the number of LDL receptors on the surface of hepatocytes, resulting in enhanced clearance of LDL-C from the bloodstream [11]. Both drugs have completed large-scale cardiovascular outcome studies, which have consistently demonstrated that both PCSK9 monoclonal antibodies are efficacious and well-tolerated therapeutic options for individuals with high

LDL-C despite maximally tolerated lipoprotein-lowering therapy. A reduction in ASCVD events achieved with evolocumab and alirocumab was proportionate to the absolute reduction in LDL-C after allowance for a delay of effect. Additionally, PCSK9 inhibitors have been found to have anti-inflammatory effects on carotid plaques, suggesting improved plaque stability [16]. These two drugs became part of the standard of care in lipidology and cardiovascular medicine after their worldwide approval in 2016 and their use is widely recommended in clinical practice guidelines [17]. In recent years, multiple meta-analyses have been published demonstrating LDL-C lowering efficacy of both PCSK9 inhibitors and, importantly, found no association with serious adverse events, such as neurocognitive dysfunction or liver enzyme elevation [18, 19].

In addition, both alirocumab and evolocumab have demonstrated less predictable efficacy in patients with HoFH, a very serious autosomal recessive condition with few available treatment options [20, 21]. Originally, it had been speculated that the precise genotype of patients with HoFH would predict responsiveness to PCSK9 inhibitors, with those having null DNA variants predicted to show no response while those having defective DNA variants predicted to have some response. Unfortunately, this has not proven to be the case. Current clinical guidelines nonetheless recommend an empirical trial of approximately 2–3 months with either of these agents in all patients with HoFH [22]. However, the anti-PCSK9 monoclonal antibodies are essentially adjunctive or bridging therapies for patients with HoFH en route to more efficacious treatments, such as evinacumab, as discussed below.

2.1.1 Evolocumab

Evolocumab is widely approved for patients with either established ASCVD, heterozygous familial hypercholesterolemia (HeFH), or HoFH. It is administered via a subcutaneous injection, with a recommended dosage of either 140 mg biweekly or 420 mg monthly. In patients with HoFH aged 10 years and older, if a clinically meaningful response is not achieved in 12 weeks, the dosage can be increased to 420 mg every 2 weeks. Evolocumab has been evaluated in an extensive clinical trials program over the past 15 years [23]. Here, we highlight some key clinical trials.

DESCARTES was a 52-week, randomized, double-blinded, placebo-controlled, phase III trial of evolocumab that enrolled 901 patients with an LDL-C ≥ 1.94 mmol/L (≥75.0 mg/dL) and a fasting TG level of 4.52 mmol/L (400 mg/dL) or lower [24]. Evolocumab was found to significantly reduce LDL-C by 57%, compared with placebo, at 52 weeks. The most common adverse events in the evolocumab group were nasopharyngitis and upper respiratory symptoms.

FOURIER was a randomized, double-blinded, placebo-controlled, cardiovascular outcomes trial of evolocumab [25]. Over 27,000 patients with stable ASCVD were included; entry criteria were LDL-C ≥ 1.8 mmol/L (≥70 mg/dL) and patients receiving statin therapy. At 48 weeks, evolocumab significantly reduced LDL-C by 59% to 0.78 mmol/L (30.2 mg/dL) and also reduced the risk of major adverse cardiovascular events by 15% compared with placebo (9.8% vs 11.3%; hazard ratio [HR] 0.85; 95% confidence interval [CI] 0.79–0.92; $P < 0.001$). There were no significant differences with respect to adverse events, including new-onset diabetes mellitus and neurocognitive events, with the exception of local injection-site reactions, which were more common with evolocumab compared with placebo (2.1% vs 1.6%) [25]. Subsequent subgroup analyses and open-label extension trials showed that evolocumab is effective for a wide range of high-risk patients and reduces not only coronary heart disease events but also ischemic stroke and peripheral arterial disease endpoints [26]. Furthermore, no long-term adverse consequences were associated with the low, sustained, on-treatment LDL-C levels between 0.7 and 0.8 mmol/L (27 and 31 mg/dL) [26].

2.1.2 Alirocumab

Alirocumab is approved for patients with established ASCVD and/or HeFH, and is also administered subcutaneously. It is typically prescribed at a dose of either 75 mg or 150 mg biweekly, with an alternative dosing option of 300 mg monthly for patients who prefer less frequent dosing. Several clinical trials attest to the value of alirocumab. For instance, the ODYSSEY LONG TERM trial was a randomized, double-blind, placebo-controlled, phase III trial involving 2341 patients with an LDL-C ≥ 1.8 mmol/L (≥70 mg/dL) and receiving statin therapy [27]. After 24 weeks, alirocumab reduced LDL-C by 61% compared with an increase of 0.8% in the placebo group. The most common adverse events were injection-site reactions.

ODYSSEY OUTCOMES was a double-blind placebo-controlled trial involving nearly 19,000 patients who had an acute coronary syndrome in the prior year and an LDL-C ≥ 1.8 mmol/L (>70 mg/dL), a non-high-density lipoprotein (HDL)-cholesterol ≥ 2.6 mmol/L (≥100 mg/dL), or an apo B-100 ≥ 0.8 g/L, while already receiving statin therapy [28]. After a mean duration of 2.8 years, alirocumab was associated with a significant reduction in both LDL-C of ~50% and of major adverse cardiovascular events by 15% compared with placebo (9.5% vs 11.1%, HR, 0.85; 95% CI 0.78–0.93; $P < 0.001$), which was essentially identical to the FOURIER results with evolocumab. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions, which were more common with alirocumab compared with placebo (3.8% vs 2.1%) [28].

Table 1 Targeted inhibitors of PCSK9

Agent	Dose	Mode of action	Main effects	Drug status	Comments
Evolocumab	140 mg SC injection q2 weeks or 420 mg q4 weeks	Monoclonal antibody	Reduces LDL-C by up to 65–70% with a reduction in cardiovascular end points	Widely approved for established ASCVD, HeFH, and HoFH	Well tolerated; adverse reactions include nasopharyngitis and injection-site reactions
Alirocumab	75 mg or 150 mg SC injection q2 weeks or 300 mg q4 weeks	Monoclonal antibody	Reduces LDL-C by up to 65% with a reduction in cardiovascular endpoints	Widely approved for ASCVD, HeFH and HoFH	Well tolerated; adverse reactions include nasopharyngitis and injection-site reactions
Inclisiran	Initial 284 mg SC injection, repeated at 3 months, then q6 months	GalNAc-conjugated siRNA	Reduces LDL-C by up to 55%	Approved for patients with HeFH and patients with ASCVD not meeting LDL-C target	ORION-4 and VICTORION-2P cardiovascular outcome trials are ongoing
Lerodalcibep	300 mg SC injection monthly	Fusion protein of *PCSK9* gene-binding domain (adnectin) and albumin	Reduces LDL-C by up to 60–65% in patients with HeFH and a high ASCVD risk	Pending likely phase III outcomes trial in patients with ASCVD; not yet approved in NA or EU	Drug is stable at ambient temperatures; safety and efficacy seem comparable to monoclonal antibodies
VERVE-101	0.1–0.6 mg/kg one-time intravenous transfusion	LNP-conjugated CRISPR base editing	LDL-C reduction of up to 73%	Development paused	Novel one-and-done treatment; enrollment has been paused after a participant experienced side effects attributed to the LNP delivery system
VERVE-102	Details pending	GalNAc-LNP-conjugated CRISPR base editing	Details pending	Enrolling for phase I trial	Potential "one-and-done" treatment; the GalNAc-LNP delivery system should reduce off-target adverse effects

ASCVD atherosclerotic cardiovascular disease, *apo* apolipoprotein, *EU* European Union, *GalNAc* N-acetylgalactosamine, *HeFH* heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol, *LNP* lipid nanoparticle, *NA* North America, *PCSK9* proprotein convertase subtilisin/kexin, *q* every, *SC* subcutaneous, *siRNA* small interfering RNA

2.2 siRNA Against *PCSK9*: Inclisiran

Inclisiran (Leqvio®) represents a novel approach to inhibiting PCSK9. It comprises a silencing siRNA conjugated to triantennary N-acetylgalactosamine carbohydrate (GalNAc) [29]. N-acetylgalactosamine carbohydrate binds to asialoglycoprotein receptor, which is highly expressed on the surface of hepatocytes. The GalNAc ligand enhances specificity to hepatocytes, thus reducing off-target effects in other tissues. Upon hepatocyte uptake, the antisense strand of inclisiran recruits an RNA-induced silencing complex to degrade *PCSK9* messenger RNA (mRNA), thus reducing LDL-C levels [29]. Inclisiran was approved by the FDA in 2021 as an adjunct treatment for adult patients with HeFH or clinical ASCVD who have not met target LDL-C levels receiving maximally tolerated statin therapy. Inclisiran is dosed at 284 mg subcutaneously initially, then again at 3 months, and then every 6 months indefinitely. Inclisiran has an active clinical trial program.

The ORION-9 phase III, randomized, double-blind, placebo-controlled trial conducted in 482 patients with HeFH showed a 44% placebo-adjusted reduction in LDL-C over and above background therapy with statin and/or ezetimibe [30]. The ORION-10 and ORION-11 trials were randomized, double-blind, placebo-controlled, phase III studies that evaluated the efficacy and safety of inclisiran in patients with ASCVD or ASCVD risk equivalents [31]. The trials included 1561 and 1617 patients respectively, with mean baseline LDL-C levels of 2.70 mmol/L (105 mg/dL) in both groups. At day 510, inclisiran reduced LDL-C levels by ~50% in both groups. Inclisiran was well tolerated; however,

local injection-site reactions were significantly more frequent in the inclisiran arm versus placebo.

The ORION-4 and VICTORION-2P trials are currently ongoing to determine the impact of inclisiran on cardiovascular outcomes, with results expected in 2025 and 2027, respectively. In the meantime, a pooled analysis of ORION-9, ORION-10, and ORION-11 found inclisiran to significantly reduce composite major adverse cardiovascular events (HR 0.75; 95% CI 0.60–0.94; $P = 0.013$) [32].

In early 2024, results from the ORION-5, randomized, phase III clinical trial were published [33]. This trial included 56 patients with HoFH with markedly elevated LDL-C receiving maximally tolerated therapy. The investigators reported that although inclisiran reduced PCSK9 levels, it did not significantly or consistently reduce LDL-C or other atherogenic lipoproteins. Although no head-to-head comparisons of inclisiran with anti-PSCK9 monoclonal antibodies were conducted, the findings suggest a potential difference in efficacy in the LDL-C reduction in patients with HoFH. Because of an inter-individual variability in response, clinical guidelines still recommend an empirical trial of PCSK9 inhibitor therapy in patients with HoFH [22]. Inclisiran has been approved by the FDA for management of the lipid profile for adults with primary hyperlipidemia, including HeFH, but not for cardiovascular disease prevention.

2.3 Adnectins

Adnectins are a class of engineered protein therapeutic agents that are derived from the fibronectin type III domain, a naturally occurring protein structure in human tissues. Adnectins are structurally similar to antibodies, but they are smaller and more stable. They can bind to specific target proteins or receptors with high affinity, making them potentially useful in treating various diseases. Because of their small size and modular structure, adnectins offer several advantages, including enhanced tissue penetration, high specificity for targets, and potentially fewer side effects compared with traditional antibodies [34].

2.3.1 Lerodalcibep

Lerodalcibep is a small recombinant fusion protein (adnectin) comprising a PCSK9-binding domain and human serum albumin. Lerodalcibep demonstrated a highly effective LDL-C reduction with monthly subcutaneous dosing of 300 mg in a 1.2-mL volume. The LIBerate-HeFH phase III trial randomized 478 subjects with HeFH (mean age 53 years, 51.7% female) who had baseline LDL-C of 3.88 ± 1.66 mmol/L (150 ± 64.2 mg/dL) taking a statin ± ezetimibe [34]. Lerodalcibep reduced placebo-adjusted LDL-C by 58.6% at 24 weeks [34]. Sixty-eight percent of lerodalcibep-treated subjects attained both a reduction in LDL-C ≥ 50% and the recommended European Society of Cardiology LDL-C target levels. Other than mild injection-site reactions, treatment-emergent adverse events were similar between lerodalcibep and placebo. Similar efficacy and safety of lerodalcibep were reported for 922 high cardiovascular-risk participants in the 52-week, randomized, controlled, phase III, LIBERATE-HR trial [35]. Lerodalcibep is not yet approved, but, depending on its approval and accessibility, may represent a promising potential new therapy for patients with HeFH.

2.4 Genome Editing

Genome editing technologies, such as the clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 system, represent a potential paradigm shift in biomedical research and therapeutic development. CRISPR/Cas9 uses a guide RNA to direct the Cas9 nuclease to a specific DNA sequence, where it creates double-stranded breaks [36]. This mechanism relies on the cell's innate DNA repair processes, which can introduce mutations or enable the insertion of new genetic material at the break site. While this approach has revolutionized research methods, its therapeutic potential was limited because of the possibility of unintended DNA modifications.

A related next-generation CRISPR system, known as base editing, uses engineered enzymes that can precisely alter DNA bases without causing double-stranded breaks [36]. This approach reduces the risk of unintended mutations or genomic instability. Base-editing technology allows for precise genetic modifications with therapeutic potential for monogenic diseases such as sickle cell anemia, cystic fibrosis, and Duchenne muscular dystrophy [37]. The technology can also be used to induce specific gene-silencing mutations. Indeed, this is the approach being applied to the *PCSK9* gene by companies such as Verve Therapeutics (Boston, MA, USA) with the goal of sustained or permanent reduction in LDL-C.

2.4.1 VERVE-101 and VERVE-102

VERVE-101 is an investigational CRISPR base-editing therapeutic agent aimed at durably inactivating the *PCSK9* gene in patients with HeFH. VERVE-101 comprises an mRNA encoding an adenine base editor and a guide RNA targeting *PCSK9*, encapsulated in a lipid nanoparticle (LNP). VERVE-101 is intended to be a single-course treatment, potentially offering a lasting solution to lower LDL-C levels. Safety and efficacy data in non-human primate and mouse models were first published in January 2023, demonstrating dose-dependent *PCSK9* gene editing in hepatocytes by up to 70% and reductions in the PCSK9 protein up to 83%

[38]. In November 2023, the interim results of VERVE-101's phase I trial were presented at the Scientific Sessions of the American Heart Association [39]. The study included ten participants with HeFH receiving maximally tolerated, oral, lipid-lowering therapy. Participants were sorted into groups with increasing doses from 0.1 mg/kg to 0.6 mg/kg. Plasma levels of PCSK9 and LDL-C were reduced by up to 84% and 55%, respectively. Two major adverse events were reported. One participant died of a cardiac arrest 5 weeks after infusion, and another patient had a myocardial infarction 1 day after the infusion. VERVE-101 has been voluntarily paused because of a grade 3 reaction of thrombocytopenia and elevated liver enzymes thought to be related to the LNP delivery system.

VERVE-102 is similar to VERVE-101 except it uses a GalNAc-LNP. The GalNAc conjugate allows for highly specific targeting of the liver via interaction with the asialoglycoprotein receptor expressed on hepatocytes. This new delivery system is anticipated to reduce off-target effects. The Heart-2 clinical trial has received regulatory clearances in Canada, Australia, and the UK, but not in the USA. The phase Ib trial is enrolling patients with HeFH or premature coronary artery disease. There are no clinical data available for VERVE-102. However, the company has announced that seven participants have been dosed so far, and they plan to present initial data in the first half of 2025 [40].

2.5 Other Approaches to Reduce PCSK9

MK-0616 is an oral macrocyclic peptide inhibitor of PCSK9 that was studied in a phase IIb trial of 380 participants in which all tested doses showed statistically significant ($P < 0.001$) differences in the percentage change in LDL-C from baseline at 8 weeks relative to placebo, with a range from −41.2% with 6 mg daily to −60.9% with 30 mg daily, and with negligible adverse effects [41].

3 Anti-Lp(a) Therapies

Lipoprotein(a), or Lp(a), is a unique, pro-atherogenic particle that is structurally related to LDL. Lp(a) is formed through a covalent bond between the distinctive apo(a) protein and apo B-100 on an LDL-like particle. The addition of apo(a) imparts proinflammatory and prothrombotic properties over and above the cholesterol within its core [42]. Lp(a) levels are genetically determined and follow a skewed distribution with elevated Lp(a) (defined as >100–125 nmol/L) in ~20% of the general European population and higher mean levels in Black and South Asian populations [43]. Elevated Lp(a) levels are associated with an increased risk of ASCVD independent of apo B-100, which represents the total level of atherogenic lipoproteins [44]. Lp(a) levels are not correlated with apo B-100, non-HDL-cholesterol, or LDL-C [45]. In clinical practice, the Canadian Cardiovascular Society guidelines recommend that Lp(a) be considered a non-modifiable risk factor similar to a positive family history of ASCVD and that Lp(a) should be measured at least once in a patient's lifetime [17]. Unlike LDL-C and apo B-100, Lp(a) levels are unaffected by lifestyle changes or statin therapy. Although niacin reduces Lp(a) levels by ~23%, outcome studies have not demonstrated a clinical benefit with respect to cardiovascular outcomes [42]. Additionally, the side-effect profile of niacin makes it intolerable for many patients when given at the usual therapeutic doses. Interestingly, PCSK9 inhibitors decrease Lp(a) levels by 15–30%; however, whether they reduce the Lp(a)-attributable ASCVD risk remains unclear [46]. Currently, no medication is approved with a specific indication for reducing elevated Lp(a) levels in patients, but here we discuss several that are under investigation. Table 2 provides a summary of the investigational anti-Lp(a) therapies discussed below.

3.1 Pelacarsen

Pelacarsen is an antisense oligonucleotide (ASO) conjugated to GalNAc. Pelacarsen preferentially targets hepatocellular apo(a) mRNA, preventing its translation and subsequent production of Lp(a). Pelacarsen was investigated in a randomized, double-blind, placebo-controlled, phase II trial of 286 patients with cardiovascular disease and Lp(a) ≥ 150 nmol/L [47]. At the 6-month mark, pelacarsen reduced Lp(a) levels by 80% with once-weekly 20-mg subcutaneous injections (the highest dose). A phase III study assessing the impact of pelacarsen-mediated Lp(a) lowering on cardiovascular events is currently underway and set for completion in May 2025 [48]. Although not investigated in the phase II study, the experimental arm involves a once-monthly 80-mg subcutaneous injection.

3.2 Olpasiran

Olpasiran, a GalNAc-conjugated siRNA, targets and degrades apo(a) mRNA, preventing the assembly of Lp(a). A phase I trial of 27 healthy Japanese participants demonstrated that olpasiran reduced Lp(a) by 56–99% without serious adverse effects [49]. The OCEAN(a)-DOSE phase II trial enrolled patients with ASCVD and elevated Lp(a). Participants received subcutaneous injections of olpasiran at 10 mg, 75 mg, or 225 mg every 12 weeks, or 225 mg every 24 weeks [50]. At week 36, significant dose-dependent Lp(a) reductions were observed, with a 97.4% reduction with the 75-mg dose. The ongoing phase III OCEAN(a)-Outcomes trial is evaluating the impact of olpasiran on cardiovascular events in patients with Lp(a) ≥ 200 nmol/L and a history of ASCVD [51]. The primary outcome is time to coronary

Table 2 Targeted inhibitors of Lp(a)

Agent	Dose	Mode of action	Main effects	Drug status	Comments
Pelacarsen	20–60 mg q4 weeks; 20 mg q2 weeks; 20 mg q1 week	GalNAc-conjugated ASO	Reduces Lp(a) levels by up to 90%	Phase III trial ongoing	Well tolerated; OCEAN(a) phase III outcomes trial expected to complete in second half of 2025
Olpasiran	225 mg SC injection q12 weeks	GalNAc-conjugated siRNA	Reduces Lp(a) by > 90%	Phase III trial ongoing	Well tolerated; Lp(a) HORIZON phase III outcomes trial expected to complete in December 2026
Lepodisiran	Single SC dose (varies)	GalNAc-conjugated siRNA	Reduces Lp(a) by > 90% for up to 48 weeks	Phase III trial ongoing	Well tolerated; ACCLAIM-Lp(a) phase III outcomes trial expected to complete in March 2029
Zerlasiran	SC 300 mg q4–8 weeks	GalNAc-conjugated siRNA	Reduces Lp(a) by > 90% for up to 48 weeks	Phase II trial completed	Well tolerated; no phase III trial at time of publication
Muvalaplin	Oral, once daily 30–800 mg doses have been tested	Small-molecule inhibitor	Reduces Lp(a) by up to 65%	Phase II trial completed	Well tolerated; once-daily oral option could satisfy patient preferences and be more affordable than injectable medications; no phase III trial at time of publication

ASCVD atherosclerotic cardiovascular disease, *ASO* antisense oligonucleotide, *GalNAc* N-Acetylgalactosamine, *Lp(a)* lipoprotein(a), *OCEAN(a)* Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction, *q* every, *SC* subcutaneous, *siRNA* small interfering RNA

heart disease death, myocardial infarction, or urgent coronary revascularization. Completion is expected in December 2026. In contrast to pelacarsen, which has once-monthly dosing, the dosing for the outcomes trial for olpasiran is once every 3 months.

3.3 Lepodisiran

Lepodisiran, like olpasiran, is an siRNA that targets apo(a) mRNA to reduce Lp(a) levels. It is also conjugated with GalNAc to enhance liver-specific uptake [52]. Lepodisiran maintains reduced Lp(a) levels for up to 1 year after a single administration, although the exact mechanism for this remains uncertain. In a phase I clinical trial of 48 adults without cardiovascular disease and with baseline Lp(a) levels > 75 nmol/L, lepodisiran resulted in a 94% reduction in Lp(a) levels after 48 weeks with the highest dose of 608 mg [51]. The trial demonstrated that lepodisiran was well tolerated, with no significant safety concerns identified. Lepodisiran is currently being investigated in a phase II study to evaluate its long-term efficacy and safety in a larger cohort, which is pending completion [53].

3.4 Zerlasiran

Zerlasiran, another siRNA targeting hepatic synthesis of the apo(a) component of Lp(a), was evaluated in a single-dose and multiple-dose phase I clinical trial of safety and tolerability in a total of 51 subjects comprising both healthy participants and patients with stable ASCVD with Lp(a) ≥ 150 nmol/L [54]. Doses ranged from 200 to 450 mg. The median baseline Lp(a) level was 288 nmol/L and median changes in the Lp(a) level at 365 days after single doses were ~30% in the single dose groups, with acute reductions of 97–99% after two doses [54]. A recent phase II clinical trial of 178 patients with ASCVD and Lp(a) levels ≥ 125 nmol/L found that zerlasiran reduced Lp(a) levels by up to 86% at week 36 when dosed at 450 mg every 24 weeks, with no serious adverse events related to the drug [55].

3.5 Muvalaplin

Muvalaplin is a first-in-class, oral, small-molecule inhibitor of Lp(a) formation, designed to disrupt the initial noncovalent binding of apo(a) kringle IV domains 7 and 8 to apo B-100 [56]. A phase I clinical trial of 114 healthy individuals with baseline Lp(a) levels ≥ 30 mg/dL demonstrated

that muvalaplin was well tolerated and resulted in placebo-adjusted Lp(a) reductions of up to 65% after 14 days [56]. A recent phase II clinical trial of 233 participants with Lp(a) levels ≥ 125 nmol/L and a high cardiovascular risk found dose-dependent placebo-adjusted Lp(a) reductions of up to 86% with the 240-mg/day dosing and no safety or tolerability concerns [57]. The once-daily administration of muvalaplin presents an alternative to injectable therapies, potentially improving patient adherence and preference.

4 Anti-Apo C-III Therapies

Approximately 25% of the population has mild-to-moderate HTG, characterized by TG levels that range from 2 to 9.9 mmol/L (from 175 to 885 mg/dL), while about 1 in 500 has severe HTG, defined as TG levels > 10 mmol/L (>885 mg/dL) [58]. Elevated TG levels result from excessive plasma TG-rich lipoproteins, primarily intestinally derived chylomicrons and/or hepatically derived very-low-density lipoproteins, as well as metabolic remnants of these species [58]. The risk to health of severe HTG from refractory chylomicronemia is acute pancreatitis, while the cholesterol within very-low-density lipoproteins and remnant particles in patients with mild-to-moderate HTG increases the risk of ASCVD [58]. Therapies effective for lowering LDL-C such as statins, ezetimibe, and inhibitors of PCSK9 are relatively ineffective for reducing TG levels [1, 58]. Historically, other classes of agents such as fibrates, niacin derivatives, and omega-3 fatty acids have been used to reduce elevated TG levels, but these have variable efficacy and have not been shown to reduce the risk of pancreatitis, and have not been found to reduce the risk of ASCVD above baseline statin therapy [1]. However, the REDUCE-IT trial demonstrated the omega-3 fatty acid derivative icosapent ethyl to reduce cardiovascular events above statins, compared with placebo [59].

Recent research has highlighted a new pharmacological target for reducing TG levels, namely apo C-III, a hepatically secreted protein that circulates on the surface of TG-rich lipoproteins and acts to suppress their lipolysis [60]. Individuals who carry disabling variants in the *APOC3* gene have naturally lower plasma TG levels and an ~40% reduced incidence of ischemic vascular disease and ischemic heart disease [61]. These observations motivated the development of new pharmacological therapies that emulate the protective effects seen in apo C-III deficiency by targeting *APOC3* mRNA to reduce apo C-III protein production. Among the agents currently available or under development to inhibit apo C-III are volanesorsen, olezarsen, and plozasiran. Table 3 provides a summary of these three targeted inhibitors of apo C-III.

4.1 Volanesorsen

Volanesorsen (Waylivra®) is a subcutaneously administered ASO that specifically targets *APOC3* mRNA within hepatocyte nuclei, thus inhibiting synthesis of apo C-III. This reduces circulating apo C-III levels by up to 90%, with concomitant dose-related decreases in TG levels. Three key clinical trials have reported the effects of volanesorsen in defined patient populations, namely the APPROACH, COMPASS, and BROADEN trials carried out in patients with familial chylomicronemia syndrome (FCS), severe HTG due to multifactorial chylomicronemia syndrome (MCS), and HTG secondary to lipodystrophy, respectively.

APPROACH was a double-blind, randomized, 52-week, phase III trial of volanesorsen in 66 adult patients with FCS who were randomly assigned to receive volanesorsen ($n = 33$) or placebo ($n = 33$) [62]. At the 3-month timepoint, patients receiving volanesorsen had a 90% decrease in plasma apo C-III levels relative to placebo and a 77% decrease in mean TG levels. However, there were tolerability issues: 20 of 33 patients who received volanesorsen had injection-site reactions compared with zero patients who received placebo. Furthermore, 15 of 33 patients who received volanesorsen had platelet counts <100,000 per microliter compared with zero patients on placebo. Two patients taking volanesorsen had platelet counts < 25,000/mL. Platelet counts recovered after drug discontinuation and enhanced platelet monitoring during the trial helped prevent severe thrombocytopenia [62]. It was speculated that patients with FCS recruited for the APPROACH trial had hepatosplenomegaly, which may have predisposed them to splenic platelet sequestration, thus increasing the risk of thrombocytopenia.

COMPASS was a double-blind, randomized, 52-week, phase III trial of adults with HTG but with MCS rather than FCS, of whom 114 were randomly assigned to receive either volanesorsen ($n = 76$) or placebo ($n = 38$) [63]. At the 3-month timepoint, volanesorsen reduced the mean plasma TG level by 71%. In safety analyses, five events of acute pancreatitis occurred during the study, all of them in three patients from the placebo group. Injection-site reactions were more frequent in the volanesorsen group compared with placebo: 24% versus 0.2%. One participant in the volanesorsen group experienced a platelet count reduction of <50,000/mL and one patient experienced serum sickness.

BROADEN was a double-blind, randomized, 52-week, phase II/III trial of 40 adult patients with lipodystrophy [64]. At the 3-month timepoint, volanesorsen reduced the mean TG level by 66% compared with placebo, accompanied by a significant 53% reduction in hepatic fat at the 12-month timepoint. There were no changes in body volume measurements, i.e., liver, spleen, visceral/subcutaneous adipose tissue, or glycosylated hemoglobin. Serious adverse events

Table 3 Targeted inhibitors of apolipoprotein C-III

Agent	Dose	Mode of action	Main effects	Drug status	Comments
Volanesorsen	300 mg SC q1 week	ASO	Reduces TG level by 50–60% in patients with FCS and 60–70% in patients with MCS	Approved in EU for FCS but not in NA	Thrombocytopenia in a substantial proportion of FCS patients
Olezarsen	50 or 80 mg SC monthly	GalNAc conjugated ASO	Reduces TG level by 45–50% and pancreatitis risk by 88% in patients with FCS	Approved in 2024 for FCS	Well tolerated; potential for less severe HTG cases is unclear; clinical dose will be 80 mg
Plozasiran	25 or 50 mg SC q12 weeks	GalNAc conjugated siRNA	Reduces TG level by 60–80% and pancreatitis risk by 83% in patients with FCS or persistent chylomicronemia	Under regulatory review; approval likely in 2025	Well tolerated; CV outcomes trial is planned; clinical dose will be 25 mg

ASO antisense oligonucleotide, *CV* cardiovascular, *EU* European Union, *FCS* familial chylomicronemia syndrome, *GalNAc* N-acetylgalactosamine, *MCS* multifactorial chylomicronemia syndrome, *NA* North America, *q* every, *SC* subcutaneously, *siRNA* small interfering RNA, *TG* triglyceride

in patients assigned to volanesorsen included one case each of sarcoidosis, anaphylactic reaction, and systemic inflammatory response syndrome. There were no cases of thrombocytopenia.

The above three studies, which were not individually powered to detect an effect on pancreatitis risk, were subsequently meta-analyzed together [65]. This revealed that 2% of patients randomized to volanesorsen had incident pancreatitis events compared with 10% of those randomized to placebo, a significant 82% reduction in pancreatitis risk (odds ratio, 0.18; 95% CI 0.04–0.82). When weighing the relative clinical benefits versus the risks of thrombocytopenia associated with volanesorsen, different regulators reacted divergently. For instance, the European Medicines Agency approved volanesorsen for the treatment of FCS, but recommended routine blood count monitoring. In contrast, the FDA rejected the application of volanesorsen because of the risk of thrombocytopenia.

4.2 Olezarsen

Olezarsen (Tryngolza® is a next-generation, subcutaneously delivered, GalNAc-conjugated ASO targeting hepatic *APOC3* mRNA [66]. This allows for lower doses of olezarsen to achieve significant clinical effects while minimizing exposure to non-hepatic tissues. This targeted approach not only enhances drug efficacy but also reduces systemic toxicity, contributing to a favorable safety profile observed in clinical trials, where mild injection-site erythema was the primary side effect.

An early-phase dose-finding study showed that after 6 months, olezarsen reduced TG levels between 23% and 60%, with the greatest reductions using the 50-mg dose every 4 weeks [66]. Nuclear magnetic resonance analysis of plasma subsequently showed favorable qualitative changes in the particle concentration of triglyceride-rich lipoprotein, LDL, and HDL following olezarsen administration, which would predict a more favorable anti-atherogenic profile [67].

Two important clinical trials have recently been published with olezarsen. The first, called BALANCE [68], was a double-blind, randomized, 52-week, phase III trial of 66 adults with FCS, of whom 22 were assigned to the olezarsen 80-mg group, 21 to the olezarsen 50-mg group, and 23 to the placebo group. Plasma TG levels at 6 months were significantly reduced with the olezarsen 80-mg dose by 43.5%, but not with the 50-mg dose. Eleven episodes of acute pancreatitis occurred in the placebo group, compared with one episode in each olezarsen group, translating to an odds ratio of 0.12 (95% CI 0.02–0.66). Adverse events of moderate severity occurred in four patients in the olezarsen 80-mg group only.

The second key trial of olezarsen, called BRIDGE [69], was a double-blind, randomized, phase IIb trial of 154 adults either with moderate HTG (defined as a TG level of 150–499 mg/dL or 1.7–5.6 mmol/L) plus an elevated ASCVD risk or with severe HTG (defined as a TG level of ≥ 500 mg/dL or ≥ 5.6 mmol/L) to receive either olezarsen 50 mg or olezarsen 80 mg. Median patient age was 62 years and median TG level was 242 mg/dL (2.73 mmol/L). The 50-mg and 80-mg doses of olezarsen significantly reduced TG levels by 49.3% and 53.1%, respectively, compared with placebo. Other pro-atherogenic lipoprotein variables also improved with treatment, while the LDL-C level was unchanged. The risks of adverse events were similar in the three treatment groups. Based on the results of this clinical research program, olezarsen was approved in late 2024 for treatment of FCS based on prophylaxis against pancreatitis, while a potential

indication for ASCVD prevention will require a larger randomized clinical trial of cardiovascular outcomes.

4.3 Plozasiran

Plozasiran is a GalNAc-conjugated siRNA that targets *APOC3* mRNA within the cytoplasm of hepatocytes [70]. Three clinical trials of plozasiran have been published to date. SHASTA-2 was a phase IIb dose-ranging trial of 226 adults with severe HTG with a mean baseline TG level of 897 mg/dL or 10.1 mmol/L [71]. At 6 months, plozasiran induced significant, dose-dependent, placebo-adjusted mean reductions in TG levels of 57%. Furthermore, 91% of plozasiran-treated patients achieved a TG level <500 mg/dL (<5.6 mmol/L), a level at which there is protection from pancreatitis. However, plozasiran was also associated with dose-dependent increases in LDL-C of up to 60%. Meanwhile, it decreased non-HDL-cholesterol and did not increase apo B-100, leaving the clinical significance of the LDL-C rise uncertain. Adverse event rates were similar in plozasiran-treated patients and placebo.

MUIR was a 48-week, double-blind, randomized, placebo-controlled, phase IIb trial evaluating the safety and efficacy of plozasiran in 353 adult patients with mixed hyperlipidemia (defined as a TG level between 150 and 499 mg/dL or 1.7 and 5.6 mmol/L, and either an LDL-C ≥ 70 mg/dL or ≥ 1.8 mmol/L, or a non-HDL-cholesterol ≥ 100 mg/dL or ≥ 2.6 mmol/L) [70]. Such a phenotype would also be consistent with what experienced lipidologists would call "combined hyperlipidemia" rather than "mixed dyslipidemia," which classically refers to former hyperlipoproteinemia type 5 [1]. Participants were assigned in a 3:1 ratio to receive plozasiran or placebo within each of four cohorts: placebo, plozasiran 10 mg, 25 mg, and 50 mg given at varying intervals. At week 24, significant reductions in the TG level were observed with plozasiran compared with placebo: 49.8%, 56.0%,. 62.4%, and 44.2% with the 10-mg quarterly dose, 25-mg quarterly dose, 50-mg quarterly dose, and 50-mg half-yearly dose, respectively. Worsening glycemic control was observed in 10%, 12%, 7%, 20%, and 21% of participants receiving placebo, 10-mg quarterly dose, 25-mg quarterly dose, 50-mg quarterly dose, and 50-mg half-yearly dose, respectively.

PALISADE was a multicenter, double-blind, placebo-controlled, phase III trial with 75 participants with persistent chylomicronemia due to genetically or clinically defined FCS despite stable standard-of-care treatment [72]. Participants were randomized to quarterly dosed plozasiran (25 or 50 mg subcutaneously) or placebo for 12 months. The baseline median TG level was 2044 mg/dL (23.1 mmol/L). Plozasiran was associated with placebo-subtracted median TG reductions at 10 months of 59% and 53% for the 25-mg and 50-mg doses, respectively ($P < 0.001$). All other key secondary endpoints showed significant responses to plozasiran, including a reduced incidence of pancreatitis (odds ratio, 0.17 [95% CI 0.03–0.94, $P = 0.03$]). The proportion of participants experiencing adverse events was similar across groups.

Based on the results of this clinical research program, approval is being sought from regulators for the use of plozasiran in patients with FCS and patients with severe HTG based on prophylaxis against pancreatitis. Additionally, a large randomized clinical trial of ASCVD outcomes with plozasiran is being planned.

5 Anti-ANGPTL3 Therapies

Angiopoietin-like 3 is part of a protein family with complex and incompletely defined effects on plasma lipoprotein metabolism [10]. Because humans with ANGPTL3 loss-of-function variants had panhypolipidemia, it was reasoned that patients with hypercholesterolemia, HTG, or especially with combined hyperlipidemia could benefit from ANGPTL3 inhibition. Three agents targeting ANGPTL3 reached advanced stages of development, but two were terminated and only one — evinacumab — is currently available for clinical use. Table 4 provides a summary of the ANGPTL3 inhibitors discussed below.

5.1 Evinacumab

Evinacumab (Evkeeza®) is a fully human monoclonal antibody against ANGPTL3 that has shown clear benefit as an LDL-lowering therapy for patients with HoFH. This drug, given intravenously at monthly intervals, is highly effective in these patients who lack LDL receptor activity; the extreme LDL-C elevations in patients with HoFH are refractory to statins and PCSK9 inhibitors and respond only to apheresis and lomitapide [1]. Evinacumab reduces LDL-C by up to 55% in patients with HoFH [73] and by up to 50% in patients with severe HeFH [74].

However, evinacumab appears to have minimal effect on TG levels in patients with FCS with biallelic loss-of-function variants and genetically absent lipolysis but is relatively more efficacious in patients with less severe HTG, for example, patients with MCS with heterozygous loss-of-function variants [75]. In patients with FCS, TG levels were unchanged with evinacumab, while LDL-C increased by 15% [75]. In MCS, evinacumab reduced TG levels by up to 80%, but absolute levels often remained markedly elevated, while LDL-C increased by > 50% [74]. Thus, targeting plasma ANGPTL3 appears to be relatively fruitless in patients with absolute lipolytic deficiency, but not in patients with a partial deficiency of lipolysis, as in MCS [10]. Despite these complex effects, evinacumab is definitely

Table 4 Targeted inhibitors of ANGPTL3

Agent	Dose	Mode of action	Main effects	Drug status	Comments
Evinacumab	15 mg/kg IV q4 weeks	Monoclonal antibody	Reduces LDL-C by up to 60% in HoFH; variable effects in HTG patients	Widely approved for HoFH	Reduces need for apheresis; evidence that it can regress atherosclerosis
Vupanorsen	80–160 mg SC q4 weeks	GalNAc conjugated ASO	Variable lowering of TG and LDL-C levels depending on metabolic background	Development terminated	Dose-related hepatosteatosis, especially in obese patients
Zodasiran	50–200 mg SC q12 weeks	GalNAc conjugated siRNA	Variable lowering of TG and LDL-C levels depending on metabolic background	Development terminated	Worsened glycemia in patients with diabetes mellitus; no clear target population
VERVE-201	0.1–3.0 mg/kg IV single infusion	Genomic DNA base editing in hepatocytes	Marked suppression of ANGPTL3 expression in pre-clinical models	Enrolling for phase I trial	Potential "one-and-done" intervention

ANGPTL3 angiopoietin-like 3 protein, *ASO* antisense oligonucleotide, *GalNAc* N-acetylgalactosamine, *HoFH* homozygous familial hypercholesterolemia, *HTG* hypertriglyceridemia, *IV* intravenously, *LDL-C* low-density lipoprotein cholesterol, *q* every, *SC* subcutaneously, *siRNA* small interfering RNA, *TG* triglyceride

a transformational drug in HoFH and was approved by the FDA and European Medicines Agency in 2021 only for the treatment of these patients.

5.2 Vupanorsen and Zodasiran

Vupanorsen is an ASO that targets *ANGPTL3* mRNA. In patients with metabolic syndrome and moderate combined hyperlipidemia, vupanorsen reduced TG and LDL-C levels by ~40% and ~12%, but also increased hepatic fat by 13–24% [76]. In such patients, vupanorsen, at doses that suppressed ANGPTL3 by > 95% reduced TG and LDL-C levels by 57% and 9%, respectively, but also increased hepatic fat by 76% and raised serum transaminase levels [77]. Vupanorsen development was halted because of the unfavorable benefit-to-harm ratio.

Zodasiran (formerly AROANG3) is an siRNA molecule that targets *ANGPTL3* mRNA in the cytoplasm. In healthy volunteers, zodasiran reduced plasma ANGPTL3, TG, and LDL-C levels by ~80%, ~55%, and ~9%, respectively, with no increase in intrahepatic fat [78]. Among patients with mild-to-moderate combined hyperlipidemia (i.e., TG level of 150–500 mg/dL or 1.7–5.6 mmol/L and LDL-C level of ≥ 70 mg/dL or ≥ 1.8 mmol/L), zodasiran given subcutaneously at doses up to 200 mg safely reduced ANGPTL3, TG, and LDL-C levels by up to 71%, 59%, and 32%, respectively, with no increased hepatic fat and even decreased hepatic fat among those with hepatosteatosis at baseline [78]. Finally, in patients with mixed or combined hyperlipidemia, zodasiran was associated with significant decreases in TG levels at 24 weeks but was also noted to increase glycosylated hemoglobin levels in patients with pre-existing diabetes [79] Zodasiran development was also halted because of the unfavorable benefit-to-harm ratio.

5.3 VERVE-201

VERVE-201 comprises an mRNA for an adenine base editor and a guide RNA that targets the *ANGPTL3* gene to severely attenuate its expression [80]. The components are packaged in a GalNAc LNP and are delivered by a single intravenous infusion. Pre-clinical data in primary human hepatocytes confirmed specific, potent, and dose-responsive *ANGPTL3* editing, while administration to various mouse models similarly showed liver editing of the *ANGPTL3* target and a reduction in blood ANGPTL3 protein levels of 98–99% [80]. The appeal of this therapy is its potential for a "one-and-done" intervention that is highly specific and targeted. VERVE-201 is initially being developed for the treatment of HoFH, which appears to be appropriate given the success of evinacumab in these challenging patients. The Pulse-1 phase Ib clinical trial investigating VERVE-201 is currently enrolling patients with refractory hypercholesterolemia and patients with HoFH, and has received regulatory clearances in Canada, Australia, and the UK [40].

6 Conclusions

The field of lipidology has been at the forefront of the evaluation of novel biological and molecular therapeutics for the treatment of patients with hyperlipoproteinemia who are either insufficiently responsive to or intolerant of standard medications such as oral statin drugs. The recurring

successful approach involves the use of human genetics to identify molecular targets whose levels can then be suppressed at the protein level by monoclonal antibodies or adnectins, at the mRNA level by ASOs or siRNAs, or at the genomic DNA level by base-editing platforms. The clearest success story has been achieved with PCSK9 inhibitors, particularly the marketed drugs alirocumab, evolocumab, and inclisiran. These are transformational therapies for many patients with dyslipidemia, including those with HeFH and those with a high ASCVD risk whose LDL-C levels cannot be adequately controlled with existing therapies. The PCSK9 target remains popular, as evidenced by ongoing development of inhibition by an adnectin (lerodalcibep) as well as genome-editing strategies such as VERVE-102.

Targeting Lp(a) by ASO, siRNA, or even with a small-molecule orally administered drug is biochemically effective, but we await the results of cardiovascular outcomes trials, particularly for pelacarsen and olpasiran, which are fairly imminent. Targeting *APOC3* mRNA, particularly with olezarsen and plozasiran, provides hope for the first time for patients with severe HTG due to FCS who live under the shadow of draconian dietary fat restriction and daily anxiety over acute pancreatitis episodes. Whether either of these agents will also have a positive impact on ASCVD risk in patients with mild-to-moderate HTG remains to be determined. Finally, ANGPTL3 inhibition had been theorized to be a potentially effective therapy for patients with combined hyperlipidemia. However, clinical experience has yielded several conclusions: (1) the monoclonal antibody evinacumab is remarkably effective in isolated, severely elevated LDL-C levels in HoFH with normal TG levels, providing hope for improved survival and reduced morbidity resulting from this rare but clinically severe hyperlipoproteinemia; (2) there is variable efficacy of evinacumab when an elevated TG level is part of the phenotype; and (3) potentially deleterious effects on *ANGPTL3* mRNA suppression when elevated TG is part of the phenotype, with the risk of hepatosteatosis with greater degrees of suppression. Finally, though significant uncertainty remains, the prospect of "one-and-done" treatments of hypercholesterolemia via genome editing targeting *PCSK9* or *ANGPTL3* offers hope for patients with these conditions and their families.

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