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REVIEW ARTICLE

Lipid-Lowering RNA Therapeutics for Atherosclerotic Cardiovascular Disease Prevention: A State–of–the–Art Review

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Abstract

Despite the modern era of effective and safe high-intensity statins and non-statin agents, a significant portion of patients are still unable to achieve guideline-recommended lipid goals for the prevention of atherosclerotic cardiovascular disease (ASCVD) events. Accordingly, novel strategies are needed to further mitigate residual risk for patients on the background of maximally tolerated lipid-lowering therapies. The past decade has seen an explosion of new agents leveraging ribonucleic acid (RNA)-based technology which reduce plasma lipoprotein levels. In this state–of–the–art review, we examine the ongoing clinical development of lipid-lowering RNA therapeutics. We discuss the efficacy and safety profiles of antisense oligonucleotides and small interfering RNA agents targeting low-density lipoprotein, lipoprotein(a), and triglyceride-rich lipoproteins. We also present challenges future clinical trials must answer to prove RNA therapeutics as a viable strategy for ASCVD prevention among patients with refractory hyperlipidemia.

Key Points

A significant portion of patients treated with maximally tolerated lipid-lowering therapy still have elevated levels of lipoproteins associated with an increased risk for ASCVD events.

The past decade has seen an explosion of new RNA therapeutics, including antisense oligonucleotides and small interfering RNA agents, which target low-density lipoprotein, lipoprotein(a), and triglyceride-rich lipoproteins.

Despite potent efficacy exhibited in clinical trials of RNA therapeutics, many patients do not achieve goal lipid levels with a single agent; combinations of RNA therapeutics could be the key to mitigating residual risk for ASCVD events and should be the area of future study.

1 Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the most common cause of death globally, and apolipoprotein B (ApoB)-containing lipoproteins are known to drive atherosclerosis [1]. Current guidelines for the prevention of cardiovascular events call for aggressive reduction in low-density lipoprotein (LDL) cholesterol concentrations and secondarily non-high density lipoprotein (non-HDL) cholesterol [2–4]. Despite the widespread availability of high-intensity statins and non-statin agents, a significant portion of patients are still unable to achieve guideline-recommended LDL cholesterol targets [5]. Recent evidence also suggests lipoprotein(a) and triglyceride-rich lipoproteins (TRLs) as potent risk modifiers for ASCVD, which are only modestly lowered with existing therapies [2, 3, 6–8]. Accordingly, novel strategies are needed to further reduce residual risk associated with elevated concentrations of these lipoproteins. In this state–of–the–art review, we examine existing ribonucleic acid (RNA)-based gene therapeutics and their role as an emerging strategy for ASCVD prevention among patients with unmet needs due to refractory hyperlipidemia.

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Table 1 Comparison of RNA therapeutics

	Antisense oligonucleotide	Small interfering RNA
Structure	Single-stranded, short chains of oligonucleotides	Double-stranded, long chains of oligonucleotides
Mechanism	Directly bind to mRNA through complementary Watson-Crick base pairing and then recruit RNAse-H	Assemble into a RISC and then full-length complementary binds to mRNA via the RNA interference pathway
Route	Subcutaneous	Subcutaneous
Peak plasma concentration	2–4 h after injection	4 h after injection
Dosing frequency	Monthly	Every 3–12 months

mRNA messenger ribonucleic acid, *RISC* RNA-induced silencing complex, *RNA* ribonucleic acid

2 Mechanisms of RNA Therapeutics

RNA therapeutics are a powerful class of pharmacotherapy agents, capable of gene silencing, editing, and expression modulation [9, 10]. Recent clinical trials for lipid-lowering therapy (LLT) have primarily evaluated two RNA approaches: antisense oligonucleotides (ASO) and small interfering RNA (siRNA). A comparison of these two RNA modalities is demonstrated in Table 1.

ASO therapeutics are single-stranded, short chains of synthetic nucleotides, also known as oligonucleotides, that bind to messenger RNA (mRNA) targets through complementary Watson-Crick base pairing [9–12]. Of note, the chemical modifications of oligonucleotides overcome the innate challenges of regular human nucleotides which are highly susceptible to intracellular nucleases, immunogenic, and increase the odds of off-target interactions [9, 10]. The specific chemical modifications of oligonucleotides are proprietary and vary by delivery platform. Once intracellular, existing ASO therapeutics recruit RNAse-H in the cytoplasm, an endogenous ribonuclease expressed ubiquitously in mammalian cells, which then mediates cleavage of the sense RNA strand, thereby inhibiting further gene translation [9–12]. Pre-clinical studies seeking to use ASOs to modulate pre-mRNA splicing or base substitution with the ultimate goal of gene editing are ongoing [9, 10]. Following administration subcutaneously, peak plasma ASO drug concentration is reached within 2–4 h [13]. With a terminal elimination half-life of approximately 4 weeks, most phase 3 trials of ASOs have utilized monthly dosing.

siRNA therapeutics are double-stranded, long chains of oligonucleotides that assemble into an RNA-induced silencing complex (RISC) and then initiate the endogenous RNA interference pathway [9, 10, 14]. RISCs rely on full-length complementary binding to catalytically degrade target mRNA [9, 10, 14]. Following administration subcutaneously, siRNA achieves a peak plasma drug concentration at approximately 4 h [15]. Despite a short terminal elimination half-life of approximately 9 h, siRNA therapeutics demonstrate very long durations of action with significant efficacy previously shown to range from 3 to 12 months, depending on the agent. Accordingly, studies of this modality utilize dosing frequencies ranging from every 3 months to yearly.

Inherent with effective gene therapy comes the most feared complication: off-target genetic modifications, including germline changes. Accordingly, a primary consideration in the development of these agents includes ensuring a high specificity for a target organ or cell type. Given the fact that free nucleic acids have poor oral bioavailability, are very susceptible to degradation in the bloodstream, and are negatively charged, limiting their ability to enter cells, agents require specially designed platforms that both stabilize nucleic acids during transport and ensure appropriate delivery [9, 10]. These platforms also permit lower dosing and injection volumes [16]. Novel lipid-lowering therapeutics have intentionally been designed to localize to the liver since the organ is the primary site of lipoprotein metabolism. Key to achieving this goal has been leveraging the asialoglycoprotein receptor (ASGPR). ASGPR is highly conserved in humans, and is densely expressed with each hepatocyte containing as many as 500,000 surface binding sites per cell [10]. Importantly, the receptor is minimally expressed in extra-hepatic tissue, mitigating the risk of off-target impacts [10]. ASGPR binds desialylated glycoproteins that exhibit non-reducing terminal galactose (Gal) or N-acetylgalactosamine (GalNAc) [17]. Once a ligand is bound, desialylated glycoproteins are rapidly endocytosed through clathrin-coated pits, and then detach when subjected to the acidic endosomal environment [9, 10]. ASGPR recycles back to the cell surface in approximately 15 min [9, 10].

Most delivery platforms of existing RNA agents for LLT rely on the direct conjugation of nucleic acid "payloads" to Gal or GalNAc ligand "warheads" [9, 10]. Once these agents are endocytosed via ASGPR, ligand warheads are cleaved off and the conjugated payload is slowly released from the endosome into the cytoplasm in a process known as "endosomal escape" [9, 10, 18]. While the exact mechanism of endosomal escape is unknown, the gradual release

of payloads is thought to explain the long duration of action for this class of agents [9, 10, 18].

With their overall durability and associated infrequent dosing promoting adherence, RNA therapeutics are emerging as potentially impactful alternatives to existing pharmacologic classes. To prevent the development of atherosclerosis, RNA therapeutics must target various lipoproteins linked with increased risk for ASCVD events.

3 Viable Targets for Atherosclerotic Cardiovascular Disease (ASCVD) Prevention

LDL and its structural surface protein, ApoB, are key targets for ASCVD prevention. Extensive evidence supports the conclusion that LDL causes ASCVD [19]. LDL particles penetrate endothelial walls of arteries, deposit their cholesterol core contents, activate macrophages, and initiate an inflammatory cascade that results in plaque formation [20]. Clinical guidelines call for aggressive lowering of LDL cholesterol for prevention of ASCVD. Contemporary LLTs reduce LDL cholesterol by inhibiting endogenous cholesterol synthesis (statins), preventing exogenous cholesterol absorption (ezetimibe), and promoting hepatic uptake of LDL particles via the LDL receptor (statins and Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors). While atherogenicity is proportional to the number of LDL particles rather than the concentration of cholesterol contained within each particle, LDL cholesterol historically serves as a frequent proxy for particle count in routine clinical practice due to its ease of measurement [21]. With each LDL particle containing one molecule of ApoB, serum ApoB concentrations are considered a better proxy of LDL particle concentration and, as such, a better predictor of ASCVD risk than calculated LDL cholesterol [22]. This conclusion has been recurrently validated, including a recent large prospective cohort analysis comprised of patients from a national biobank as well as multiple international clinical trials that found risk of MACE to be most highly associated with ApoB level, independent of lipid content levels [23–25]. A sub-study of the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial found that major adverse cardiovascular events (MACE) increased with higher ApoB, and patients with larger reductions in ApoB had a lower risk of MACE, even after adjusting for cholesterol concentrations [26]. Reduction of serum ApoB levels, and, therefore, LDL particle concentration, reduces the risk of cardiovascular events.

Lipoprotein(a) (Lp(a)), an LDL particle with a single apolipoprotein(a) (Apo(a)) attached, is a potential target of novel therapies for the prevention of ASCVD. Plasma Lp(a) levels are predominantly (70–90%) determined genetically as opposed to resulting from lifestyle or environmental exposure [27, 28]. Lp(a) was identified as an independent risk for ASCVD events using large epidemiologic and genetic studies [29–31]. Mendelian randomization studies have found absolute reductions of Lp(a) by approximately 125–215 nmol/L to be associated with similar clinical benefits as a reduction in LDL cholesterol by 38.7 mg/dL [32–34]. More recently, results from large clinical trials have further supported the association of elevated Lp(a) concentrations with ASCVD events. Among statin-treated patients with ASCVD enrolled in FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk), the randomized control trial that compared evolocumab with placebo, patients with baseline Lp(a) in the highest quartile (> 165 nmol/L) had a higher risk for ASCVD events or urgent revascularization compared with those in the lowest quartile [35]. A meta-analysis of patient-level data from seven randomized, placebo-controlled, statin outcomes trials including 29,029 statin-treated patients with a high baseline ASCVD risk showed that patients with elevated Lp(a) concentrations had higher risk for ASCVD events compared with patients with low Lp(a) levels [36]. In a post hoc analysis of ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), higher Lp(a) levels in patients with recent acute coronary syndromes were associated with a higher ASCVD event rate regardless of whether LDL cholesterol levels were < 70 or > 70 mg/dL [37]. Furthermore, lowering of Lp(a) appears to be beneficial: in another post hoc analysis of ODYSSEY Outcomes, even a 1 mg/dL reduction in Lp(a) mass was found to be associated with a significantly decreased risk for ASCVD events with a hazard ration (HR) of 0.994 (95% confidence interval (CI): 0.990–0.999) [38]. At the population level, a recent analysis of the Family Heart Database, which consists of American medical claims between 2012 and 2022 from 340 million individuals, found that the increased risk for recurrent ASCVD events attributed to elevations in Lp(a) levels ≥ 180 nmol/L can be mitigated with PCSK9 inhibitors [39]. Multiple questions remain, including: whether lowering Lp(a) with agents specifically targeting this lipoprotein actually yields fewer ASCVD events; what is defined as an elevated Lp(a) level; when should clinicians intervene; and what are the criteria for initiation of Lp(a) pharmacotherapy and treatment targets?

Triglyceride-rich lipoproteins (TRLs), including chylomicrons, chylomicron remnants, very low-density lipoprotein (VLDL), and intermediate density lipoprotein, are another emerging target for ASCVD prevention [40]. Recent work by Johannesen et al. found that the risk associated with ApoB may actually exceed that associated with LDL cholesterol. They suggested that this excess ApoB risk can be accounted for by TRLs that also contain ApoB on their surfaces [41]. Other evidence supports TRLs as independently associated

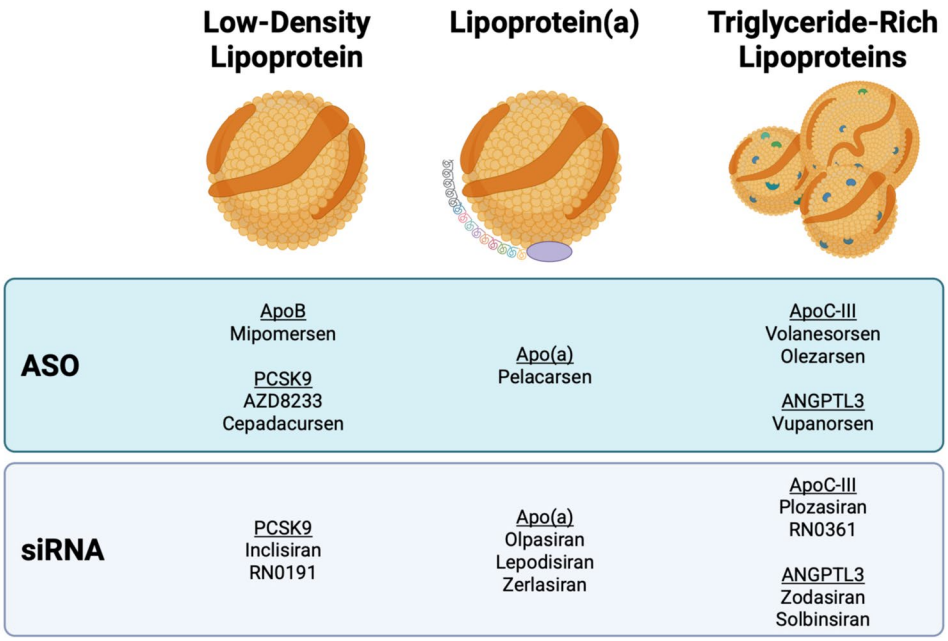

Fig. 1 The past decade has seen an explosion of new RNA therapeutics, including antisense oligonucleotides (ASO) and small interfering RNA (siRNA) agents. Existing drugs target various steps in the lipid metabolism pathway, thereby causing dramatic reductions in low-density lipoprotein, lipoprotein(a), and triglyceride-rich lipoproteins. Supposing combinations of RNA therapeutics are feasible, successful combinations will aim to silence distinctive targets within the lipoprotein metabolism pathway to produce desired effects. *ANGPTL3* angiopoietin-like protein 3, *Apo(a)* apolipoprotein(a), *ApoB* apolipoprotein B, *ApoC-III* apolipoprotein C-III, *PCSK9* proprotein convertase subtilisin/kexin type 9

with ASCVD progression, including a UK Biobank study that directly compared the impact between TRLs/remnants and LDL cholesterol and ASCVD [42, 43]. Using a Mendelian analysis of lipoprotein-associated single nucleotide polymorphisms, they reported TRLs/remnant lipoproteins to have substantially greater atherogenicity per particle than LDL, even when adjusting for ApoB [43]. There is also clinical outcomes trial evidence supporting the lowering of TRL/remnant levels as a means of ASCVD risk prevention [40]. REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), a large, randomized control trial of patients with established ASCVD or diabetes with an additional risk factor and residual hypertriglyceridemia, examined the impact of 4 g daily of a highly concentrated version of the omega-3-fatty acid, eicosopentaenoic acid (EPA) [44]. This trial included patients with fasting triglyceride levels between 150 and 500 mg/dL (1.7–5.6 mmol/L) who were already taking statin therapy. They found that EPA therapy resulted in both significant lowering of TRL concentrations and reduction in ASCVD events, including a 0.9% absolute risk reduction of mortality [44].

4 Existing Lipid-Lowering RNA Therapeutics

Multiple RNA therapeutics for LLT are currently under development. This section discusses existing agents and their associated ongoing trials, categorized by lipoprotein target (Fig. 1).

4.1 Low-Density Lipoproteins

Given ample evidence supporting a causal relationship between LDL and atherosclerosis, RNA therapeutics have been developed that disrupt LDL particle assembly and metabolism (Table 2).

Mipomersen was the first RNA therapeutic to be approved for LLT in the USA. A second-generation ASO, mipomersen blocks the translation of mRNA for ApoB. RADICHOL 1 (Study to Assess the Safety and Efficacy of ISIS 301012 (Mipomersen) in Homozygous Familial Hypercholesterolemia; NCT00607373) was a phase 3 randomized controlled trial evaluating the efficacy of mipomersen among patients with homozygous familial hypercholesterolemia (FH) [45]. A total of 51 subjects were randomized to receive mipomersen 200 mg subcutaneously every week or placebo [45]. At 26 weeks, the mean percentage change in LDL cholesterol of – 24.7% (95% CI – 31.6 to – 17.7) with mipomersen was significantly greater compared to placebo

Table 2 Efficacy of low-density lipoprotein cholesterol (LDL-C)-lowering agents

	mRNA target	Modality	Dosing frequency	LDL-C reduction* (%)	TG reduction* (%)	Lp(a) reduction* (%)	Development status
Inclisiran	PCSK9	siRNA	Loading dose at 12 weeks then every 24 weeks	– 48 to – 53	– 12 to – 18	– 17 to – 26	FDA approved
Mipomersen	ApoB	ASO	Weekly	– 21 to – 49	– 18 to – 35	– 23 to – 31	Discontinued
AZD8233	PCSK9	ASO	Every 4 weeks	– 62	–	–	Phase 2 NCT04964557
Cepadacursen	PCSK9	ASO	–	–	–	–	Phase 2a NCT04164888
RN0191	PCSK9	siRNA	Every 4 weeks	– 51 to – 55	–	–	Phase 1 NCT06132360

ASO antisense oligonucleotide, *FDA* US Food and Drug Administration, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *PCSK9* Proprotein Convertase Subtilisin/Kexin type 9, *siRNA* small interfering RNA, *TG* triglycerides

*Placebo-adjusted mean change from baseline respective lipid level

at – 3.3% (95% CI – 12.1 to 5.5; $p = 0.0003$) [45]. Adverse events were common among the mipomersen group only, including injection-site skin reactions (76% vs. 24% with placebo) and increases in alanine aminotransferase concentration of three times or more the upper limit of normal (12% vs. 0% with placebo) [45].

Following this study, another phase 3 trial (NCT00794664) evaluating mipomersen was conducted among patients with severe hypercholesterolemia on maximally tolerated LLT and not undergoing LDL apheresis [46]. Patients were included who had fasting LDL cholesterol ≥ 200 mg/dL and ASCVD or LDL cholesterol ≥ 300 mg/dL [46]. A total of 58 subjects were randomized to receive mipomersen 200 mg subcutaneously every week or placebo [46]. At 26 weeks, the mean percentage change in LDL cholesterol with mipomersen was significantly greater at – 36% (95% CI – 51.3 to – 15.3) compared to an increase with placebo of 12.5% (95% CI – 10.8 to 35.8; $p < 0.001$) [46]. Adverse events were common among the mipomersen group only, including injection-site skin reactions (90% vs. 32% in placebo), increases in alanine aminotransferase concentration of three times or more the upper limit of normal (28% vs. 0% in placebo), and hepatic steatosis (13% vs. 0% in placebo) [46].

In 2013, mipomersen was approved by the FDA (US Food and Drug Administration) for use in homozygous FH patients, though the medication carries a black box warning for hepatoxicity, and its use is restricted by a federal risk evaluation and mitigation strategy program [47]. The drug is no longer available in the USA, and the European Medicines Agency never approved it out of concern for adverse events.

Inclisiran, however, has proven widely successful and has been rapidly integrated into the armamentarium for LLT. A GalNAc-conjugated siRNA molecule, inclisiran silences the translation of PCSK9 mRNA, thereby up-regulating LDL receptor density on hepatocytes. Inclisiran has been studied with multiple phase 3 trials, including ORION-9 (Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol in Subjects With Heterozygous Familial Hypercholesterolemia and Atherosclerotic Cardiovascular Disease), ORION-10 (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol), and ORION-11 (Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol), all of which randomized patients to receive either inclisiran 284 mg subcutaneous injection or placebo on day 1, day 90, and every 6 months thereafter for 540 days [48]. ORION-9 evaluated patients with heterozygous FH, ORION-10 evaluated patients with ASCVD, and ORION-11 evaluated patients with ASCVD and ASCVD risk equivalents. A pooled, patient-level analysis of 3660 patients in these trials found a mean placebo-corrected change in LDL cholesterol with inclisiran of – 50.7% (95% CI – 52.9% to – 48.4%; $p < 0.0001$) at day 510 [48]. Aside from predominantly mild injection site reactions that were more frequent with inclisiran than placebo (5.0% vs 0.7%), no other significant adverse events were noted [48].

VICTORION-INITIATE (A Randomized Study to Evaluate the Effect of an "Inclisiran First" Implementation Strategy Compared to Usual Care in Patients With Atherosclerotic Cardiovascular Disease and Elevated LDL cholesterol Despite Receiving Maximally Tolerated Statin Therapy) was an open-label, phase 3b trial of 450 patients with ASCVD and LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL and fasting triglycerides < 500 mg/dL who were randomized to either usual care or usual care plus inclisiran ("inclisiran first") [49]. Patients in the inclisiran-first group received inclisiran 284 mg subcutaneously on day 1, day 90, and at day 270 [49]. At day 330, the mean percentage

change in LDL cholesterol was significantly greater among the inclisiran-first group with – 60% (97.5% CI – 65% to – 55%) compared to a – 7% (97.5% CI: – 12% to – 2%; p < 0.001) change in the usual-care group [49]. Statin discontinuation was less frequent in the inclisiran-first group compared to the usual-care group with a difference between groups of – 11% (97.5% CI: – 18% to – 3%) [49]. Importantly, LDL cholesterol goals of < 70 mg/dL and < 55 mg/dL were achieved among 82% and 72% of the inclisiran-first group, respectively, compared to 22.2% and 9% in the usual-care group, respectively ($p < 0.001$ for both LDL cholesterol goals) [49]. While treatment-emergent adverse events (TEAEs) and serious TEAE rates compared similarly between groups, injection site reactions were more frequent with the inclisiran-first group compared to the usual-care group (10% vs. 0%) [49]. Real-world evidence indicates patients prescribed inclisiran have improved adherence and persistent usage compared to those given anti-PCKS9 monoclonal antibodies (mAbs) at 12 months post-initiation; these findings suggest selecting the siRNA agent instead of mAbs could prevent approximately 28% more ASCVD events [50].

Inclisiran was FDA-approved in 2021 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous FH or clinical ASCVD who require additional LDL cholesterol lowering. Notably, the FDA prescriber information label highlights that the drug's impacts on cardiovascular morbidity and mortality have not yet been determined. However, cardiovascular clinical outcomes trials of inclisiran are ongoing trials, including ORION-4 (Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease) and VICTORION-2P (Randomized, Double-blind, Placebo-controlled, Multicenter Trial, Assessing the Impact of Inclisiran on Major Adverse Cardiovascular Events in Participants With Established Cardiovascular Disease) [2].

ORION-4 (NCT03705234) randomized 16,124 participants with ASCVD and LDL cholesterol ≥ 100 mg/dL on maximally tolerated LLT (except for PCSK9 inhibitors) to inclisiran sodium 300 mg or placebo on day 1, day 90, and every 6 months thereafter for 5 years [2]. The primary endpoint is a composite of major adverse cardiovascular events (MACE), including coronary heart disease death, nonfatal MI, fatal or non-fatal ischemic stroke, or urgent coronary revascularization procedure [2]. The study is estimated to be completed in July 2026. VICTORION-2P (NCT05030428) randomized 17,004 participants with ASCVD and LDL cholesterol ≥ 70 mg/dL on maximally tolerated LLT (including high-intensity statins and excluding PCSK9 inhibitors) to inclisiran sodium 300 mg or placebo on day 1, day 90, and every 6 months thereafter for 6 years [2]. The primary endpoint is time to a composite of MACE, including cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke [2]. Other ongoing outcomes trials include VICTORION-1 P (Study of Inclisiran to Prevent Cardiovascular Events in High-Risk Primary Prevention Patients) among high-risk primary prevention patients (NCT05739383) [51].

AZD8233 (ION449), Cepadacursen (CiVi 007), and RN0191 are three other RNA therapeutics with LDL-lowering potential under development. AZD8233 is a GalNAc-conjugated ASO which inhibits the translation of mRNA for PCSK9 [52]. SOLANO (Study to Assess the Safety, Efficacy and Tolerability of AZD8233 Treatment in Participants With Hyperlipidaemia) evaluated the safety of efficacy of AZD8233 6 mg subcutaneously dosed monthly among 411 patients with baseline LDL cholesterol ≥ 70 mg/dL but < 190 mg/dL on maximally tolerated LLT (NCT04964557) [53]. While the study's primary endpoint was safety, LDL cholesterol reduction with AZD8233 was reported as – 62.3% at 28 weeks [54]. However, the therapeutic's manufacturer has decided not to advance into phase 3 development [54]. Cepadacursen is another ASO that inhibits the translation of mRNA for PCSK9. A phase 2a randomized, placebo-controlled trial (NCT04164888) evaluated cepadacursen among patients with ASCVD and LDL cholesterol ≥ 70 mg/dL or LDL cholesterol ≥ 100 mg/dL on maximally tolerated LLT [55]. In total, 49 patients were randomized to receive either cepadacursen at one of three different dosing regimens or placebo. The incidence of adverse events was the trial's primary endpoint, and percent change in LDL cholesterol at 1 and 2 months were secondary endpoints. While the study was completed at the end of 2021, results are still not public at the time of this publication. An oral formulation of cepadacursen (CiVi 008) is currently undergoing pre-clinical testing [56]. RN0191 is a siRNA which inhibits the production of PCSK9 [57]. Early results from a phase 1 trial among 32 healthy patients with serum LDL cholesterol ≥ 100 mg/dL randomized to a single subcutaneous injection of RN0191 (dose ranging from 60 mg to 600 mg) or placebo noted LDL cholesterol reductions of – 51% to – 55% from baseline at 21–28 days. The study is expected to be completed in 2025 [58].

4.2 Lipoprotein(a)

Multiple RNA therapeutics are being studied that inhibit the translation of apolipoprotein(a) mRNA, thereby preventing the assembly of Lp(a) particles in hepatocytes (Table 3).

Pelacarsen, a GalNAc-ligand conjugated ASO molecule, was the first agent to complete phase 2 testing. Investigators randomized 286 patients with ASCVD and Lp(a) ≥ 60 mg/dL (150 nmol/L) to receive one of five dosing regimens of pelacarsen or placebo [59]. At 6 months, pelacarsen significantly reduced Lp(a) levels in a dose-dependent manner, with the highest dosing regimen resulting in a – 80% reduction in Lp(a) compared to – 6% with placebo [59]. Aside

Table 3 Efficacy of lipoprotein (a) (Lp(a))-lowering agents

	mRNA target	Modality	Dosing frequency	LDL-C reduction* (%)	TG reduction* (%)	Lp(a) reduction* (%)	Development status
Pelacarsen	Apo(a)	ASO	Every 1 to 4 weeks	– 5 to – 20	0 to – 10	– 29 to – 74	Phase 3 NCT04023552
Olpasiran	Apo(a)	siRNA	Every 12 to 24 weeks	– 23 to – 25	–	– 71 to – 101	Phase 3 NCT05581303
Lepodisiran	Apo(a)	siRNA	Every 26 to 52 weeks	– 6 to – 12	0	– 41 to – 94	Phase 3 NCT06292013
Zerlasiran	Apo(a)	siRNA	Every 16 to 24 weeks	– 25 to – 32	+3 to – 4	– 81 to – 86	Phase 2 NCT05537571

Apo(a) apolipoprotein(a), *ASO* antisense oligonucleotide, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *siRNA* small interfering RNA, *TG* triglycerides

*Placebo-adjusted average change from baseline respective lipid level

from primarily mild injection-site reactions (27% vs. 6% placebo), adverse events associated with pelacarsen included urinary tract infection (13% vs. 6% placebo), myalgia (12% vs. 11% placebo), and headache (11% vs. 8% placebo) [59]. A phase 3 cardiovascular outcomes trial of pelacersen, Lp(a) HORIZON (Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients With CVD), is currently ongoing and includes 8,323 patients with ASCVD and Lp(a) ≥ 60 mg/dL (≥ 175 nmol/L) who received pelacarsen 80 mg subcutaneously every month (NCT04023552). The trial seeks to determine if Lp(a) reduction with pelacersen prevents MACE, and trial results are expected to be announced in 2025.

Olpasiran is a GalNAc ligand-conjugated siRNA molecule aiming to lower Lp(a) levels. The agent was evaluated in OCEAN(a)-DOSE (Olpasiran Trials of Cardiovascular Events And Lipoprotein(a) Reduction – DOSE Finding Study), a phase 2 trial in which investigators randomized 281 patients with established ASCVD and Lp(a) ≥150 nmol/L to receive one of four dosing regimens of olpasiran or placebo.[34] At 36 weeks, Lp(a) concentration was reduced by olpasiran in a dose-dependent manner, including a placebo-adjusted mean percent change of – 100.5% (95% CI: −105.2% to −95.8%) in the highest dose group (olpasiran 225mg every 24 weeks).[34] Aside from mostly mild injection-site reactions, no other adverse events were detected with olpasiran.[34] A phase-3 cardiovascular outcomes trial of olpasiran, OCEAN(a)-Outcomes (Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction – Outcomes Trial), is currently ongoing and includes 7297 patients with ASCVD and Lp(a) ≥200 nmol/L who received olpasiran every twelve weeks (NCT05581303). The trial seeks to determine if Lp(a) reduction with olpasiran prevents MACE and is expected to be completed at the end of 2026.

Lepodisiran (LY3819469) is another GalNAc ligand-conjugated siRNA molecule that silences Apo(a) production, and it is designed to be long acting. In its phase 1 trial, patients without ASCVD and Lp(a) ≥ 75 nmol/L were administered a single injection of lepodisiran (one of six doses) or placebo [60]. At 48 weeks, the highest dose group reduced Lp(a) by a median – 94% (interquartile range (IQR) – 94% to – 85%) compared to a maximal median reduction of – 5% (IQR – 16% to 11%) in the placebo group [60]. Aside from injection-site reactions, two patients in the lepodisiran group had elevations in liver enzymes greater than three times the upper limit of normal, and there was a single serious adverse event of a facial injury after a fall from a bicycle that occurred 141 days after injection [60]. The phase 2 trial of lepodisiran was also recently completed; 320 patients with Lp(a) ≥ 175 nmol/L were randomized to receive one of four dosing regimens of lepodisiran or placebo [61]. They found that the highest dose (lepodisiran 400 mg) resulted in a placebo-adjusted time-averaged percent change from baseline in the serum Lp(a) concentration from day 60 to day 180 of – 93.9 percentage points [61]. None of the serious events experienced by patients in the trial were deemed to be related to lepodisiran or placebo, and 3% of patients who received lepodisiran were found to have elevations in liver enzymes greater than three times the upper limit of normal [61]. Of note, a single dose of lepodisiran 400 mg resulted in a placebo-adjusted time-averaged percent reduction in serum Lp(a) from day 30 to day 360 of 88.5 percentage points [61]. A phase 3 cardiovascular outcomes trial of lepodisiran is currently recruiting (NCT06292013). ACCLAIM-Lp(a) (Study to Investigate the Effect of Lepodisiran on the Reduction of Major Adverse Cardiovascular Events in Adults With Elevated Lipoprotein(a)) plans to recruit 15,000 patients with ASCVD and Lp(a) ≥ 175 nmol/L. The trial seeks to determine if Lp(a) reduction with lepodisiran prevents MACE, and is expected to be completed in 2029.

A third siRNA agent under development for Lp(a) reduction is zerlasiran. The agent recently completed its phase 2 trial, ALPACAR-360 (Evaluate SLN360 in Participants With Elevated Lipoprotein(a) at High Risk of Atherosclerotic Cardiovascular Disease Events), which included 178 patients with ASCVD and Lp(a) ≥ 125 nmol/L who were randomized to receive one of three dosing regimens of zerlasiran or placebo [62]. At 36 weeks, the placebo-adjusted time-averaged percent change with the highest dose of zerlasiran was −85.6% (95% CI − 90.9% to − 80.3%) [62]. Aside from predominantly mild injection-site reactions, the most common side effects were urinary tract infections, headache, and nasopharyngitis [62]. None of the serious adverse events detected in the study were considered related to zerlasiran [62]. At the time of this publication, no phase 3 trials of zerlasiran have been announced.

Of note, non-RNA therapeutics that disrupt the molecular assembly of disrupt Lp(a) particles rather than Apo(a) expression are also under development. Muvalaplin is an oral agent that specifically inhibits the interaction between Apo(a) and ApoB. The agent was recently evaluated in the phase 2 trial KRAKEN (Study of LY3473329 in Adult Participants With Elevated Lipoprotein(a) at High Risk for Cardiovascular Events), which included 233 patients with Lp(a) ≥ 175 nmol/L and ASCVD, diabetes, or FH who were randomized to receive one of three doses of muvalaplin or placebo [63]. Among the highest dose group, muvalaplin resulted in a placebo-adjusted reduction of Lp(a) concentration by – 85.8% (95% CI – 83.1% to – 88.0%) [63]. Adverse events were similar among patients treated with muvalaplin or placebo [63]. A phase 3 trial of muvalaplin has yet to be announced at the time of this publication. Other oral, small molecule Lp(a) inhibitors are also being developed, including YS2302018 [64]. The interaction between Apo(a) and ApoB is a potential target of future RNA therapeutics aiming to reduce Lp(a) levels.

4.3 Triglyceride-Rich Lipoproteins

Existing RNA therapeutics aiming to reduce TRLs target important proteins involved in their production and breakdown (Table 4).

ApoC-III inhibits lipoprotein lipase (LPL), reduces hepatic lipase activity, and prevents peripheral tissue uptake of TRLs [40, 65–68]. Recent evidence suggests apoC-III also promotes TRL formation by increasing hepatic TG mobilization and utilization during assembly as well as increasing secretion into the bloodstream [40, 69]. An analysis of the Exome Sequencing Project from the National Heart, Lung, and Blood Institute similarly found a 40% risk reduction for ASCVD among carriers of loss-of-function (LOF) variants of the *APOC3* gene compared to noncarriers of the genetic mutations [70]. The development of inhibitors against apoC-III has stepwise progressed from familial chylomicronemia syndrome (FCS) to mixed hyperlipidemia with moderate hypertriglyceridemia to prove efficacy in lowering TG and TRLs [40].

Volanesorsen is an ASO that inhibits the translation of apoC-III mRNA. The agent was first studied among patients with FCS, a rare autosomal recessive condition in which severe hypertriglyceridemia results from complete lack of LPL activity due to biallelic germline pathogenic variants, in APPROACH (Study of Volanesorsen (Formerly IONIS-APOCIIIRx) in Patients With Familial Chylomicronemia Syndrome) [66]. The trial included 66 patients and found a 77% reduction in mean TG levels, and a 46% reduction in non-HDL cholesterol levels with volanesorsen compared with an increase of 18% and 12%, respectively, in the placebo group [66]. Adverse events included injection-site skin reactions (61%) and thrombocytopenia less than 100,000 per microliter (48%) in the volanesorsen group [66]. In COMPASS (A Study of Volanesorsen (Formally ISIS-APOCIIIRx) in Patients with Hypertriglyceridemia), 114 patients with a fasting TG of 500 mg/dL or greater were randomized to receive either volanesorsen 300 mg or placebo [71]. Patients who received volanesorsen experienced a 71% reduction in mean TG levels and a 27% reduction in non-HDL cholesterol levels compared with a reduction of 0.9% and 0.8% respectively, in the placebo group [71]. Aside from injection-site skin reactions, there was an episode of thrombocytopenia and an episode of serum sickness in the volanesorsen group [71]. This agent has been approved in Europe for treatment of FCS but not in North America, due to concerns with thrombocytopenia.

Olezarsen, a third-generation, GalNAc ligand-associated ASO, was first evaluated among FCS in the phase 3 study BALANCE (Study of Olezarsen [Formerly Known as AKCEA-APOCIII-LRx] Administered to Patients with Familial Chylomicronemia Syndrome) [16]. The trial included 66 patients with FCS and fasting TG > 880 mg/dL who were randomized to receive one of two doses of olezarsen or placebo [16]. Patients who received the highest dose of olezarsen experienced a – 44 percentage point difference in mean TG levels compared to placebo [16]. Importantly, the olezarsen pooled dose group resulted in a significant reduction in acute pancreatitis episodes compared to placebo [16]. Olezarsen was then assessed among a mixed hyperlipidemia population in Bridge–TIMI 73a (Study of Olezarsen (Formerly Known as AKCEA-APOCIII-LRx) in Adults with Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease (Established or at Increased Risk for), and/or With Severe Hypertriglyceridemia), which included patients with either moderate hypertriglyceridemia (fasting TG 150-499 mg/dL) and increased risk for ASCVD

Table 4 Efficacy of triglyceride-rich lipoproteins (TRLs)-lowering agents

	mRNA target	Modality	Dosing frequency	LDL-C reduction* (%)	TG reduction* (%)	Lp(a) reduction* (%)	Development status
Volanesorsen	ApoC-III	ASO	Weekly	+91 to +130	– 70 to – 94	–	Phase 3 NCT02211209 NCT02300233, EMA Approved
Olezarsen	ApoC-III	ASO	Every 4 weeks	+26 to +57	– 44 to – 53	–	Phase 3, NCT04568434 NCT05355402
Plozasiran	ApoC-III	siRNA	Every 12 to 24 weeks	– 14 to +98	– 44 to – 63	–	Phase 3, NCT05089084 NCT04720534 NCT04998201
RN0361	ApoC-III	siRNA	–	–	–	–	Phase 1 NCT06471543
Vupanorsen	ANGPTL3	ASO	Every 8 to 16 weeks	– 8 to – 16	– 41 to – 57	–	Discontinued
Zodasiran	ANGPTL3	siRNA	Every 12 weeks	– 14 to – 20	– 51 to – 63	– 7 to – 20	Phase 2b NCT04832971
Solbinsiran	ANGPTL3	siRNA	Every 12 weeks	0 to – 12	– 36 to – 53	–	Phase 2 NCT05256654

ANGPTL3 Angiopoietin-like protein 3, *ApoC-III* apolipoprotein C-III, *ASO* antisense oligonucleotide, *EMA* European Medicines Agency, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *siRNA* small interfering RNA, *TG* triglycerides

*Placebo-adjusted mean change from baseline respective lipid level

or severe hypertriglyceridemia (fasting TG ≥ 500 mg/dL) [72]. Increased risk for ASCVD was defined as having a pre-existing clinical diagnosis of ASCVD, diabetes mellitus type 2, or a history of at least two additional ASCVD risk factors [72]. A total of 154 patients were randomized to receive either one of two doses of olezarsen or placebo [72]. At 6 months, patients who received the highest dose of olezarsen experienced a – 57% reduction in mean TG levels and a – 18% reduction in non-HDL cholesterol levels compared with a decrease of – 8% and increase of 5.6% respectively, in the placebo group [72]. No significant differences were detected in the rate of adverse events or serious events between olezarsen and placebo [72]. While no cardiovascular outcomes trials have of olezarsen have been announced, an ongoing sub-study of NCT05610280 is evaluating atherosclerotic coronary plaque progression and the development of subclinical atherosclerosis by coronary computed tomography angiography among 1,478 patients with either moderate hypertriglyceridemia and increased risk for ASCVD or severe hypertriglyceridemia.

Plozasiran is a siRNA that disrupts ApoC-III mRNA translation. The agent was studied among patients with genetically confirmed FCS or symptomatic persistent chylosevere hypertriglyceridemia (TG ≥ 880 mg/dL) in PALISADE (Study of ARO-APOC3 (Plozasiran) in Adults with Familial Chylomicronemia Syndrome) which randomized 75 subjects to one of two doses or placebo [73]. At 10 months, plozasiran resulted in a reduction of TG by – 78% in the highest dose group, compared to – 17% in the placebo group ($p < 0.001$) [73]. Notably, the incidence of acute pancreatitis was reduced in the plozasiran group (odds ratio, 0.17; 95% CI: 0.03–0.94; $p = 0.03$) [73]. The agent was also studied in 226 patients with severe TG > 500 mg/dL during the phase 2 trial, SHASTA-2 (Study to Evaluate ARO-APOC3 in Adults with Severe Hypertriglyceridemia) [74]. Patients who received the highest dose of plozasiran had a – 78% reduction in median TG levels and a 22% reduction in non-HDL cholesterol levels compared with reductions of – 17% and – 1.5%, respectively, in the placebo group [74]. No significant differences in rates of adverse events were detected in either of these trials [73, 74]. MUIR (Study of ARO-APOC3 in Adults with Mixed Dyslipidemia) evaluated the effect of plozasiran among patients with mixed hyperlipidemia, including moderate hypertriglyceridemia (TG 150-499 mg/dL) and either LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL [75]. A total of 353 patients were randomized to receive one of four dosing regimens of plozasiran (10, 25, 50 mg quarterly, 50 mg half-yearly) or matched placebo [75]. Patients who received the highest dose of plozasiran quarterly experienced an – 64% reduction in mean TG levels and a – 27% reduction in non-HDL cholesterol levels compared with a reduction of – 1.7% and – 2.7%, respectively, in the placebo group [75]. Plozasiran at the highest dose resulted in worsening glycemic control

in 20% compared to 10% in the placebo group, which the study's authors theorize was due to increased glucogenesis utilizing free fatty acids, although a homeostasis model assessment of insulin resistance did not find changes to insulin sensitivity in the plozasiran groups [75]. No thrombocytopenia episodes were reported [75]. A proposed phase 3 cardiovascular outcomes trial of plozasiran, CAPITAN, will study the agent in patients with mixed hyperlipidemia and residual risk of ASCVD [76].

RN0361 is a new siRNA that inhibits the production of ApoC-III currently under development by Rona Therapeutics. A phase 1 trial (NCT06471543) among 60 healthy patients with fasting TG > 80 mg/dL and LDL cholesterol ≥ 70 mg/dL is planned. The study is expected to be completed in 2026 [77].

Angiopoietin-like 3 (ANGPTL3) is another target of RNA therapeutics that reduce TRLs. ANGPTL3 inhibits both LPL and endothelial lipases as well as prevents hepatic uptake of TRLs. Accordingly, patients with LOF variants in *ANGPTL3* have not only enhanced LPL and endothelial lipase activity, but also a hypolipidemic phenotype, with lower levels of TRLs, LDL, and Lp(a) [78]. In an analysis of 58,000 individuals in the DiscovEHR human genetics study, those with LOF variants of *ANGPTL3* also had a 41% lower risk of ASCVD [79]. Another Mendelian randomization study using exome sequencing data from over 180,000 individuals found heterozygous carriers of *ANGPTL3* LOF variants to have a 34% reduction in odds of ASCVD [80]. ANGPTL3 was first pharmacologically targeted by a human mAb, evinacumab, which reduced LDL cholesterol levels by 49% among patients with homozygous FH, prompting it be FDA-approved for LDL cholesterol lowering only in this patient population [81]. A similar LDL-lowering effect was observed when the drug was trialed among patients with refractory hypercholesterolemia, in which 72% of included patients had heterozygous FH [82]. Evinacumab notably also lowered triglyceride levels by 50%, and a post hoc analysis of three randomized control trials of evinacumab found remnant cholesterol to be reduced by > 50% at the highest doses [81, 83]. RNA therapeutics are now being developed that target ANGPTL3 for TRL reduction, including the ASO agent, vupanorsen. TRANSLATE-TIMI 70 (A Dose-Ranging Study With Vupanorsen) was a phase 2b trial in which 286 patients with moderate hypertriglyceridemia (TG 150–500 mg/dL) and non-HDL cholesterol ≥ 100 mg/dL were randomized to receive one of seven dosing regimens of vupanorsen or placebo [84]. At 24 weeks, TG levels were lowered by – 41% to – 57%, and non-HDL cholesterol was significantly reduced by – 22% to – 28%, depending on the dosing regimen [84]. Adverse events were more common in the vupanorsen group, including elevations to greater than three times the upper limit of normal in alanine aminotransferase and aspartate aminotransferase of up to 33% and 44%, respectively [84]. Despite the trial meeting its primary endpoints, concerns for hepatotoxicity led to discontinuation of further studies of the agent [84].

Zodasiran is an siRNA agent that inhibits ANGPTL3 mRNA translation. The recently completed ARCHES-2 (Study of ARO-ANG3 in Adults With Mixed Dyslipidemia) evaluated the effect of zodasiran among patients with moderate hypertriglyceridemia (triglycerides 150–499 mg/dL) and either LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL [78]. A total of 204 patients were randomized to receive zodasiran (50, 100, or 200 mg) subcutaneously or matched placebo [78]. Patients who received the highest dose of zodasiran experienced a least-squares mean difference in reduction versus placebo in triglyceride (TG) levels of – 63%, – 36% in non-high density lipoprotein (HDL) cholesterol levels, and – 22% in ApoB [78]. Glycated hemoglobin levels were transiently elevated in the highest dose zodasiran group among patients with a pre-existing history of diabetes mellitus [78]. Development of zodasiran is paused pending future funding for this asset.

Solbinsiran is another GalNAc-conjugated siRNA that targets hepatic ANGPTL3 that recently completed its phase 2 trial. In PROLONG-ANG3 (A Study of LY3561774 in Participants With Mixed Dyslipidemia), 205 patients with mixed dyslipidemia (defined as triglycerides 150–499 mg/dL, LDL cholesterol ≥ 70 mg/dL, and non-HDL cholesterol ≥ 130 mg/dL) to receive either one of three doses of solbinsiran or placebo [85]. The primary endpoint was change in ApoB level. At day 180, they found that patients who received the middle dose of solbinsiran (400 mg) experienced a placebo-adjusted percent change in ApoB concentration from baseline of – 14.3% [85]. Of note, no significant difference in ApoB was detected among the patients who received the highest dose (800 mg) at day 180; however, at day 270, there was a statistically significant placebo-adjusted reduction in ApoB of – 10.9% in this dose group [85]. Importantly, the highest dose group of solbinsiran also showed significant reductions in serum triglycerides (-53%), VLDL cholesterol (-50%), non-HDL cholesterol (-24%), and LDL cholesterol (-12%) [85]. No differences in the incidence of adverse events between solbinsiran and placebo were detected [85]. Three patients had increases in alanine aminotransferase concentration of three times or more the upper limit of normal, and three patients had increases in aspartate aminotransferase concentration of three times or more the upper limit of normal [85].

Angiopoietin-like 4 (ANGPTL4) inhibits LPL similar to ANGPTL3. Loss-of-function variants of *ANGPTL4* are associated with both lower plasma TG levels and a reduced risk of ASCVD (odds ratio of 0.81) [86]. An ASO targeting ANGPTL4 was evaluated in mice, and the agent resulted in a 28–37% reduction in TG levels as well as significant reductions in very-low density lipoprotein and LDL cholesterol

levels [87]. However, a monoclonal antibody targeting ANGPTL4 resulted in the development of abdominal and mesenteric lymphadenopathy in mice and monkeys [86]. A phase 1/2a study with a GalNAc-lined ASO targeting *ANGPTL4* mRNA is currently underway with plans to enroll 24 patients [88, 89].

5 Are RNA Therapeutics the Silver Bullet?

With the extensive development of RNA therapeutics for LLT over the past decade, an important question remains: Are these medications the answer we have been looking for to prevent ASCVD? As previously noted, despite FDA approval of some of these agents in select groups of patients, RNA therapeutics have yet to successfully show a reduction in cardiovascular outcomes. With multiple phase 3 trials planned to be completed in the near future, we eagerly await evidence of a meaningful impact of these agents on ASCVD events.

Concerns still remain regarding residual risk mitigation for refractory hyperlipidemia patients treated with RNA therapeutics. Refractory hyperlipidemia is defined as the inability to achieve guideline-recommended lipid goals with maximally tolerated LLTs. Even with the profound effects exhibited in clinical trials of RNA therapeutics, many patients still had lipid levels above goal. For example, a substantial portion of patients who received inclisiran had refractory hypercholesterolemia. In VICTORION-INITIATE, 18% of patients in the inclisiran-first group did not achieve an LDL cholesterol < 70 mg/dL [49]. Furthermore, 28% of patients in the inclisiran-first group did not accomplish an LDL cholesterol concentration of < 55 mg/dL, the recommended goal for high-risk patient with ASCVD per the most recent expert consensus decision pathway (ECDP) [49]. Similar findings were noted in ORION-3, in which 21% of patients did not achieve LDL cholesterol < 70 mg/dL and 38% did not achieve LDL cholesterol < 50 mg/dL [90].

While more research is needed to determine a goal Lp(a) as mentioned above, the most recent ECDP does list ≥ 125 nmol/L (≥ 50 mg/dL) as a risk-enhancing factor for ASCVD. In phase 2 testing of pelacarsen in which all patients had baseline Lp(a) ≥ 60 mg/dL (150 nmol/L), 19% of patients who received the highest monthly dose did not achieve an Lp(a) level of < 50mg/dL (< 125 nmol/L) at 6 months [59]. Accordingly, even with potent RNA therapeutics that inhibit Apo(a) synthesis, a subset of patients will likely be considered refractory with a persistently elevated Lp(a) following agent administration.

Refractory hypertriglyceridemia is also observed in trials following treatment with RNA therapeutics that target TRLs. Goals for TRL level, which are quantified indirectly by measurement of serum TG concentration, vary based on the risk for acute pancreatitis and ASCVD: the most recent ECDP recommends TG lowering to < 500 mg/dL among all adult patients and < 150 mg/dL for those at high risk for ASCVD [91]. In PALISADE, where the baseline median TG level among FCS patients was 2,044 mg/dL (IQR 1,333–2,955) and the highest dose of plozasiran resulted in a median reduction of – 78% (IQR – 88 to – 49), 25% of patients did not achieve TG < 880 mg/dL and 50% did not achieve TG < 500 mg/dL, thereby meaning a considerable portion of patients still remained at an elevated risk for pancreatitis [73, 92]. In BALANCE, which was conducted with a similar patient population as PALISADE, the baseline mean TG level was 2,630 mg/dL, and patients who received the highest dose of olezarsen had a median reduction of – 34% (IQR – 54 to – 9], likewise leaving many patients above TG goal of <500 mg/dL [16]. Furthermore, in MUIR, which included patients with moderate hypertriglyceridemia (TG 150–499 mg/dL) and either LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL, depending on the dose regimen, 8–23% of patients did not achieve TG < 150 mg/dL at 24 weeks [75]. Similarly, in Bridge–TIMI 73a, which evaluated a comparable patient population to MUIR (TG 150–499 mg/dL and increased risk for ASCVD or TG ≥ 500 mg/dL), 7–14% of patients did not achieve TG < 150 mg/dL at 6 months [72].

Complicating matters further is that patients with dyslipidemias frequently have multiple lipoproteins implicated. For example, patients with heterozygous FH are known to have elevations in Lp(a) levels, irrespective of FH-causing genetic variant [93–95]. As such, lowering LDL cholesterol with an RNA therapeutic like inclisiran may achieve LDL cholesterol goals but insufficiently reduce serum Lp(a) concentration, despite the fact that inclisiran (similar to PCSK9 monoclonal antibodies) also lowers Lp(a) by 17–26% [48].

6 Future Considerations—Combinations of RNA Therapies

Due to concerns for refractory hyperlipidemia and mixed dyslipidemias, combining multiple RNA therapeutics should be an area of future study. All aforementioned trials of RNA therapeutics did not include patients who were also taking other ASO or siRNA therapies. As such, questions remain over both the safety and efficacy associated with using multiple RNA therapeutics at once. A thorough investigation of drug-drug interactions is required to ensure that new toxicities or off-target effects do not arise with simultaneous use of multiple agents. With most current agents leveraging the ASGPR for drug delivery, another theoretical concern is if a single agent completely saturates the aforementioned

Table 5 Illustrative combinations of RNA therapeutics

Hypothetical patient	mRNA targets	Agents	LDL-C reduction* (%)	TG reduction* (%)	Lp(a) reduction* (%)
Heterozygous FH + normal Lp(a)	PCSK9 + ANGPTL3	Inclisiran, zodasiran	– 55 to – 62	– 57 to – 70	– 23 to – 41
Heterozygous FH + elevated Lp(a)	PCSK9 + Lp(a)	Inclisiran, olpasiran	– 60 to – 65	– 12 to – 18	– 76 to – 100
Familial chylomicronemia syndrome + normal Lp(a)	ApoC-III + ANGPTL3	Olezarsen, zodasiran	+8 to +26	– 73 to – 83	– 7 to – 20
Familial chylomicronemia syndrome + elevated Lp(a)	ApoC-III + ANGPTL3 + Lp(a)	Plozasiran, solbinsiran, lepodisiran	– 38 to +98	– 80 to – 116	– 41 to – 94
Mixed hyperlipidemia + normal Lp(a)	PCSK9 + ANGPTL3	Inclisiran, solbinsiran	– 48 to – 65	– 48 to – 71	– 17 to – 26
Mixed hyperlipidemia + elevated Lp(a)	PCSK9 + ANGPTL3 + Lp(a)	Inclisiran, zodasiran olpasiran	– 66 to – 72	– 57 to – 70	– 78 to – 100

Hypothetical agent combinations and their presumed drug efficacy utilizing summative results from the individual agent trials; no available existing clinical trial evidence of these combinations

ANGPTL3 angiopoietin-like protein 3, *Apo(a)* apolipoprotein(a), *ApoC-III* apolipoprotein C-III, *ASO* antisense oligonucleotide, *FH* familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *PCSK9* Proprotein Convertase Subtilisin/Kexin type 9, *siRNA* small interfering RNA, *TG* triglycerides

*Placebo-adjusted average change from baseline respective lipid level

receptors on hepatocytes, thereby preventing the uptake of additional agents. However, with evidence showing rapid dissociation of ligands from ASGPR and recycling back to the cell surface, it is possible that this limitation could be overcome by allowing for sufficient time between agent administration. There is also the question of whether multiple agents are able to leverage the same endogenous gene-editing machinery at the same time. Extensive study of the pharmacokinetics of these agents working in tandem is necessary.

Supposing combinations of RNA therapeutics are feasible, we envisage clinical lipidologists needing to closely scrutinize a patient's specific lipoprotein phenotype to create an optimal LLT regimen. Successful combinations will aim to silence distinctive mechanistic targets within the lipoprotein metabolism pathway in order to create the desired lipoprotein reduction (Table 5). For patients with heterozygous FH and elevated Lp(a), agents inhibiting both PCSK9 and Apo(a) would be warranted. The combination of inclisiran with olpasiran may result in an LDL cholesterol reduction of – 60% to – 65% and an Lp(a) decrease of – 76% to – 100%, assuming drug efficacy is summative (opposed to synergistic). For patients with heterozygous FH without elevated Lp(a), a strategy inhibiting PCSK9 and ANGPTL3 with inclisiran with zodasiran or solbinsiran, respectively, which reduces LDL cholesterol by – 55% to – 62%, could also be pursued. A combination of agents inhibiting ApoC-III and ANGPTL3 may be ideal for patients with FCS and/or multifactorial chylomicronemia syndrome (MCS). Olezarsen or plozasiran combined with zodasiran would be expected to lower TG by – 73% to – 86%. Patients with mixed hyperlipidemia with elevations in all three lipoprotein types may even necessitate triple therapy targeting PCSK9, ANGPTL3, and Apo(a): inclisiran, zodasiran, and olpasiran would be anticipated to reduce LDL cholesterol by – 66% to – 72%, TG by – 57% to – 70%, and Lp(a) by – 78 to – 100%. The possibilities are nearly endless – combinations of these potent and durable agents could be the key to ensuring all patients achieve goal lipid levels.

7 Conclusion

RNA therapeutics are potent, durable, and safe lipoprotein-lowering agents. By targeting various steps in the lipid metabolism pathway, they are capable of causing dramatic reductions in LDL cholesterol, TRLs, and Lp(a). We eagerly await results from large cardiovascular clinical outcomes trials that prove this pharmacologic class to be ready for prime time as the newest tool in our arsenal for ASCVD prevention. Further study is needed to demonstrate the feasibility of combinations of RNA therapeutics to mitigate residual risk in patients with refractory and mixed dyslipidemias.

Declarations

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Authors' Contributions SDM wrote the manuscript. RSR supervised and edited the manuscript. All authors read and approved the final manuscript.

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