INTERNATIONAL JOURNAL OF CARDIOVASCULAR RESEARCH & INNOVATION
Oct-Dec 2025, VOL. 3, ISSUE 4, pp. 29-36
https://doi.org/10.61577/ijcri.2025.1000020

RESEAPRO JOURNALS

REVIEW

OPEN ACCESS

Advances in RNA based therapeutics for atherosclerosis: From bench to bedside

Oluwapelumi Vincent Arowosaye

Department of Medicine and Surgery,College of Medicine University of Ibadan, Ibadan, Nigeria

ABSTRACT

Despite advances in statin therapy and other lipid-lowering agents, atherosclerosis continues to drive a substantial global burden of cardiovascular disease (CVD). RNA-based therapeutics, including small interfering RNA (siRNA) and antisense oligonucleotides (ASOs), are emerging as innovative tools with the potential to complement or even redefine current treatment strategies. This review aims to provide clinicians with an up-to-date overview of RNA-based therapies targeting atherosclerotic CVD, with a focus on their clinical relevance, efficacy, safety, and future applications. Inclisiran, a siRNA targeting PCSK9, has recently entered clinical practice, offering effective LDL-C reduction with just twice-yearly dosing, an approach that may enhance long-term adherence and outcomes. Other RNA-based agents in clinical development target lipoprotein(a), apolipoprotein C-III, and angiopoietin-like protein 3 (ANGPTL3), addressing lipid fractions that were previously difficult to modify. Additionally, RNA platforms are being explored to modulate inflammatory pathways implicated in plaque progression, such as IL-6 and NLRP3. These therapies present promising new options for high-risk patients, particularly those with statin intolerance, familial hypercholesterolemia, or elevated lipoprotein(a). As these agents progress throughClinicians should become familiar with this evolving class of treatments as they move from specialized use toward broader clinical adoption.

KEY WORDS

RNA therapeutics; Atherosclerosis; PCSK9 inhibitors; Lipoprotein(a); Cardiovascular prevention; Clinical innovation

ARTICLE HISTORY

Received 25 November 2025;
Revised 17 December 2025;
Accepted 26 December2025

Introduction

Atherosclerosis is a disease that is characterized by the accumulation of lipids, fibrous elements, and calcification within the large arteries. This process is initiated by endothelium activation, followed by a cascade of events, which implies the vessel narrowing and activation of inflammatory pathways leading to atheroma plaque formation [1].

Atherosclerosis is not, as was often previously assumed, an irreversible process, causing disease by slow development of narrowing of the arterial lumen. Instead, the inflammation typical of atherosclerostic lesions, like other inflammatory and autoimmune diseases such as rheumatoid arthritis, can be ameliorated and also regress. Furthermore, CVD is related more to plaque rupture and atherothrombosis than to a passive thickening of the vessel wall. Atherosclerotic lesions prone to rupture are characterized by increased expression of proinflammatory cytokines as tumour necrosis factor-α (TNF-α) and γ-interferon (IFN-γ) and thus an activated immune response [2]. ASCVD (ACD) includes two major conditions: ischemic heart disease (IHD) and cerebrovascular disease (mainly ischemic stroke). IHD and stroke are the world's first and third causes of death, respectively, causing 247.9 deaths/100,000 persons in 2013, representing 84.5% of cardiovascular deaths and 28.2% of all-cause mortality. Other less prevalent complications of atherosclerosis include atherosclerosis of the aorta and peripheral vascular disease [3]. Globally, ~9.0 million deaths due to IHD in 2021 with the age-standardized death rate ~108.7 per 100,000 population [4]. According to the 2023 World Heart Report, IHD and stroke accounted for ~85% of all CVD deaths worldwide; IHD ~9.1 million deaths in 2019 [5].

The current therapies used in the treatment of atherosclerosis include Statins (HMG-CoA reductase inhibitors), which lower hepatic cholesterol synthesis leading to a reduction in LDL receptor expression. This ultimately leads to a drop in LDL-C. This is a first-line therapy for prevention of ASCVD. Other therapies include Anti-inflammatory therapies (e.g., IL-1β antibody, low-dose colchicine) and Antiplatelet / Antithrombotic therapies which target the inflammatory component of atherosclerosis and are used to prevent thrombotic events (MI, stroke) on the background of atherosclerotic plaques that rupture or erode respectively. As effective as these therapies have been, they have not been without their limitations. Many patients do not reach target LDL-C levels or still have high residual risk despite statins [6]. Statin intolerance (muscle symptoms, liver enzyme elevation) limits use in some [7]. Some risk of new-onset diabetes is associated with statin use. Anti-inflammatory therapies are newer and the evidence base is smaller compared to statins. Because atherosclerosis is multifactorial, targeting inflammation alone may not fully prevent plaque progression. They do not directly modify the underlying atherosclerotic plaque biology (lipid deposition, inflammation, smooth muscle cell change) and they are adjuncts, not cures for atherosclerosis.

RNA-based therapeutics are a class of medical treatments that use ribonucleic acid (RNA) molecules to modify, regulate, or replace gene expressions in order to treat or prevent diseases. Unlike traditional drugs that act on proteins, RNA therapeutics act upstream at the genetic level, that is, they influence how proteins are produced inside the cell. RNA-based therapeutics can be classified by the mechanism of

***Correspondence:** Mr. Oluwapelumi Vincent Arowosaye, Department of Medicine and Surgery, University of Ibadan College of Medicine, Ibadan, Nigeria, e-mail: arowosayepelumi2@gmail.com

activity, and include inhibitors of mRNA translation (antisense), the agents of RNA interference (RNAi), catalytically active RNA molecules (ribozymes), and RNAs that bind proteins and other molecular ligands (aptamers) [8].

RNA therapeutics include mRNA therapeutics / vaccines: deliver messenger RNA (mRNA) that cells translate into protein (vaccines, cancer vaccines, protein replacement), siRNA (RNA interference): short duplex RNAs that guide RISC to degrade target mRNA (gene knockdown), ASOs: single-strand oligos that alter splicing, block translation, or trigger RNase H degradation, miRNA mimics / inhibitors, aptamers, and RNA-guided editors (ADAR-recruiting guides, CRISPR-based RNA editors). RNA-targeting drugs have been developed for diseases with significant unmet medical needs through selective mRNA knockdown or modulation of pre-mRNA splicing. Recently, RNA editing, particularly antisense RNA-guided adenosine deaminase acting on RNA (ADAR)-based programmable A-to- I editing, has emerged as a powerful tool to manipulate RNA to enable correction of disease- causing mutations and modulate gene expression and protein function. Beyond correcting pathogenic mutations, the technology is particularly well suited for therapeutic applications that require a transient pharmacodynamic effect, such as the treatment of acute pain, obesity, viral infection, and inflammation, where it would be undesirable to introduce permanent alterations to the genome. This review aims to provide clinicians with an up-to-date overview of RNA-based therapies targeting ASCVD, with a focus on their clinical relevance, efficacy, safety, and future applications [9-12].

RNA-Based Therapeutic Platforms

RNA-based therapeutic platforms are technologies that employ various classes of RNA molecules to regulate gene activity, enable the synthesis of therapeutic proteins, or suppress genes responsible for disease. These platforms constitute the basis of contemporary RNA medicine and are developed to intervene at the genetic and molecular levels rather than directly targeting proteins. In comparison with traditional protein-targeted and DNA-based therapies, RNA-based therapeutics are considered promising because of their unique physicochemical and physiological characteristics. RNA operates within the three fundamental biological macromolecules: DNA, RNA, and proteins [13]. Most RNA-based drugs that are clinically approved or undergoing development are ASOs or double-stranded RNA molecules known as short interfering RNAs (siRNAs). Both ASOs and siRNAs interact with target mRNAs or pre-mRNAs through complementary Watson–Crick base pairing, but they differ in structure and mechanisms of action [14]. The commonly used RNA-based therapeutic platforms include

Antisense oligonucleotide (ASOs)

ASOs are chemically engineered, single-stranded synthetic DNA or RNA molecules designed to bind specific RNA sequences via complementary base pairing, and they have been investigated as therapeutic tools for numerous diseases. After an ASO binds to its designated RNA target, multiple molecular outcomes can occur, ranging from altered mRNA processing to complete removal of the transcript. ASOs can bind complementary sites on pre-mRNA, thereby affecting the recruitment of splicing factors and reshaping splicing outcomes. They may also bind mature mRNA to obstruct ribosome access, thereby reducing protein synthesis. Furthermore, some ASOs trigger RNase H activity on RNA–DNA hybrids, resulting in selective degradation of the target transcript [14].

Short interfering RNA (siRNA)

siRNAs are short (~21–25 nucleotide), double-stranded RNA molecules that exploit the endogenous RNAi) pathway to selectively suppress mRNA expression [15]. Mechanistically, the siRNA duplex is transported into the cytoplasm, where it is loaded onto Argonaute 2 (Ago2) to assemble the RNA-induced silencing complex (RISC). Within this complex, the “guide” strand of the siRNA directs RISC to a complementary mRNA sequence. When RISC binds to the target mRNA at specific, perfectly matched sites, Ago2 mediates endonucleolytic cleavage of the transcript, resulting in mRNA degradation and subsequent inhibition of protein translation [16,17]. siRNA–target interactions are highly sequence-specific and can distinguish between mRNAs differing by only a single nucleotide (17). Acting downstream of transcription, siRNA therefore represents a potent post-transcriptional gene-silencing strategy.

Messenger RNA (mRNA)-based approaches

mRNA-based strategies allow endogenous cellular machinery to synthesize therapeutic proteins or antigens, providing innovative solutions for diseases previously regarded as difficult or impossible to treat. These therapies function by delivering synthetic mRNA into cells, enabling transient expression of proteins for therapeutic or prophylactic purposes. In contrast to DNA-based approaches, mRNA does not integrate into the host genome, thereby minimizing the risk of insertional mutagenesis and permitting controlled, short-term protein production. Major advantages include rapid and flexible manufacturing, efficient cellular transfection, and the capacity to modulate previously “undruggable” biological targets [18,19]

Delivery systems

GalNAc conjugation for hepatocyte targeting

Tri-antennary N-acetylgalactosamine (GalNAc) ligands are chemically linked to oligonucleotides such as siRNAs or ASOs. GalNAc exhibits strong affinity for the asialoglycoprotein receptor (ASGPR), a high-capacity receptor selectively expressed on hepatocytes, thereby promoting receptor-mediated endocytosis and efficient intracellular delivery of the oligonucleotide payload [20]. ASGPR is predominantly localized on the sinusoidal surface of liver parenchymal cells and is expressed at substantially higher levels in the liver than in other tissues. This restricted expression pattern forms the basis for ASGPR-driven, liver-specific drug delivery [21]. GalNAc conjugation is particularly effective due to its strong hepatocyte selectivity and favorable pharmacokinetic and pharmacodynamic (PK/PD) properties. It supports subcutaneous dosing without reliance on large nanoparticle carriers and enables prolonged target suppression lasting weeks to months, depending on oligonucleotide chemistry. Clinical PK/PD studies and population-based modelling further demonstrate consistent hepatic uptake and sustained pharmacological effects across multiple GalNAc-siRNA compounds. Approved clinical examples include givosiran (GIVLAARI®, for acute hepatic porphyria) and inclisiran (LEQVIO®, targeting PCSK9), both of which illustrate how GalNAc technology supports infrequent dosing schedules ranging from monthly to twice-yearly administration [22,23].

Lipid nanoparticles (LNPs)

Lipid nanoparticles are nanoscale vesicles, typically 50–150 nm in

https://doi.org/10.61577/ijcri.2025.1000020

diameter, composed of ionizable or cationic lipids, cholesterol, helper lipids, and polyethylene glycol (PEG) lipids. They encapsulate RNA molecules, protecting them from nuclease-mediated degradation [24]. LNPs were instrumental in the development of mRNA-based COVID-19 vaccines and have since emerged as a dominant platform for mRNA delivery. Their strengths include robust RNA protection, modular and tunable formulation design, and suitability for large-scale manufacturing. Crucially, ionizable lipids promote endosomal escape following cellular uptake, facilitating efficient release of RNA into the cytosol where it can exert its biological function.

Viral vectors / virus-derived systems

These approaches employ viruses, or virus-derived particles, engineered to be replication-deficient and capable of delivering RNA or RNA-encoding constructs into target cells. Common examples include adeno-associated virus (AAV) and lentiviral vectors, as well as virus-like particles (VLPs) adapted for RNA delivery [24].

Extracellular vehicles (EVs) / exosomes / biological membrane-derived carriers

Extracellular vehicles (EVs) have attracted significant interest as RNA delivery vehicles due to their natural ability to encapsulate and protect RNA molecules while enabling targeted transfer to recipient cells. Their inherent biocompatibility and endogenous targeting features make them particularly attractive for therapeutic applications, especially for the efficient delivery of RNA-based medicines [24].

Clinically approved RNA therapeutics for atherosclerosis

Inclisiran

Inclisiran (Leqvio®) is a first-in-class siRNA therapeutic developed by Novartis for the management of hypercholesterolaemia. Synthetic siRNAs exploit the endogenous RNAi mechanism to selectively suppress the expression of specific genes. Inclisiran is a long-acting synthetic siRNA designed to target the mRNA of proprotein convertase subtilisin/kexin type 9 (PCSK9) and is conjugated to triantennary N-acetylgalactosamine (GalNAc) moieties. This GalNAc conjugation strategy enables highly specific uptake by hepatocytes. PCSK9, a protein largely produced in the liver, represents an important therapeutic target in hypercholesterolaemia due to its central role in lipid metabolism and regulation of circulating cholesterol levels [25]. The identification of PCSK9 as a serine protease that enhances degradation of the low-density lipoprotein (LDL) receptor provided a novel pathway for controlling plasma LDL cholesterol concentrations. Early therapeutic strategies aimed at lowering PCSK9 levels primarily involved monoclonal antibodies, which function by binding circulating PCSK9 within the reticuloendothelial system and preventing its interaction with the LDL receptor. Because circulating PCSK9 originates almost exclusively from hepatic synthesis, approaches that inhibit liver-specific PCSK9 production present a viable alternative to antibody-based therapies [26,27]. Inclisiran received approval in the European Union on 9 December 2020 for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to dietary modification [25,26] It is indicated for use alongside statins, or statins combined with other lipid-lowering agents, in patients who fail to achieve target low-density lipoprotein cholesterol levels with maximally tolerated statin therapy. In individuals who are intolerant to statins or for whom statins are contraindicated, inclisiran may be administered as monotherapy or in combination with other lipid-lowering treatments [25].

Key phase-3 trial results ORION-10 and ORION-1

Design

Two randomized, placebo-controlled phase-3 trials (ORION-10 conducted in the United States and ORION-11 conducted in Europe and other regions) enrolled patients with established ASCVD or heterozygous familial hypercholesterolaemia (HeFH) who were receiving maximally tolerated statin therapy but required additional LDL-C reduction. Inclisiran was administered subcutaneously at a dose of 284 mg at baseline, again at 3 months, and subsequently every 6 months. The primary efficacy endpoint assessed the percentage change in LDL-C at approximately day 510 (around month 17) [28].

Efficacy

Inclisiran produced a mean LDL-C reduction of approximately 50% compared with placebo across both ORION-10 and ORION-11 trials, with sustained lipid lowering maintained through twice-yearly dosing. While the magnitude of reduction varied depending on analytical methods and baseline treatments, observed decreases generally ranged between ~45–52% [28].

Safety (headline)

The overall incidence of adverse events was comparable between the inclisiran and placebo groups, with the exception of a higher frequency of injection-site reactions among inclisiran-treated patients, which were predominantly mild to moderate in severity. Across the pivotal randomized trials, no consistent signals indicating major safety concerns were identified [28].

Regulatory status / indications

Inclisiran was approved by the U.S. Food and Drug Administration on 22 December 2021 as an adjunct to diet and maximally tolerated statin therapy for adults with HeFH or clinical ASCVD requiring further LDL-C reduction. Approval in the European Union was granted in December 2020, followed by additional authorizations worldwide. The recommended dosing schedule is 284 mg administered subcutaneously at day 0, at 3 months, and subsequently every 6 months [29].

Real-world evidence from early post-approval registries and implementation studies suggests that inclisiran use in routine clinical practice results in rapid and substantial reductions in LDL-C levels, often closely matching those reported in clinical trials. Observational programs, including V-INITIATE, VICTORIAN, and other cohort studies, demonstrate marked improvements in guideline-recommended LDL-C goal attainment, with reported rates increasing from approximately 20% under standard care to nearly 80% following initiation of inclisiran therapy [30]. Safety outcomes observed in real-world settings are consistent with trial data, with injection-site reactions remaining the most common adverse events, systemic effects occurring infrequently, and no unexpected safety signals reported to date, although the duration of follow-up remains shorter than that available for long-established oral lipid-lowering agents [31].

https://doi.org/10.61577/ijcri.2025.1000020

RNA Therapies in Late-Stage Clinical Development

RNA therapies for lipoprotein(a) (Lp[a])

Elevated Lp(a) is an independent and largely genetically determined risk factor for ASCVD and aortic stenosis; conventional lipid-lowering therapies, including statins and PCSK9 inhibitors, exert only modest or inconsistent effects on Lp(a) levels.

Pelacarsen

Pelacarsen is a GalNAc-conjugated antisense oligonucleotide (ASO) developed to reduce circulating lipoprotein(a) by selectively inhibiting hepatic synthesis of apolipoprotein(a). Following subcutaneous administration, the GalNAc ligand binds the asialoglycoprotein receptor (ASGPR) expressed on hepatocytes, enabling efficient receptor-mediated uptake and directing the ASO to the primary site of LPA mRNA expression. Within hepatocytes, the single-stranded ASO hybridizes through complementary base pairing to a specific sequence on LPA mRNA, forming an RNA–DNA duplex that is recognized by RNase H1. RNase H1 cleaves the RNA strand of the duplex, resulting in degradation of the LPA transcript and subsequent suppression of apo(a) translation. This mechanism leads to reduced hepatic apo(a) production, impaired assembly of Lp(a) particles which require covalent binding of apo(a) to apoB-100–containing lipoproteins and sustained reductions in plasma Lp(a) concentrations with repeated dosing [32–35]. Pelacarsen is a second-generation ASO incorporating chemical modifications, including triantennary N-acetylgalactosamine, which enhance metabolic stability, reduce off-target toxicity relative to earlier ASOs, and permit rapid, hepatocyte-specific uptake at the site of apo(a) synthesis. In a phase 2b clinical study, pelacarsen achieved reductions in Lp(a) concentrations of ≥80% with a favorable safety profile in patients with established ASCVD [32].

Late-stage/outcome trial

The Lp(a) HORIZON trial (NCT04023552) is a pivotal phase-3 cardiovascular outcomes study designed to determine whether pelacarsen-mediated lowering of Lp(a) translates into reduced ASCVD events in patients with established CVD and elevated Lp(a). Results are pending, and HORIZON is expected to provide the first definitive evidence on whether pharmacological reduction of Lp(a) improves clinical outcomes [33].

Clinical-outcome implication (current)

Although pelacarsen has demonstrated consistent and robust Lp(a) lowering in early-phase trials, its capacity to reduce myocardial infarction or stroke remains under evaluation in HORIZON. Thus, while Lp(a) reduction is a well-established biological effect, it is not yet a confirmed event-reducing therapeutic strategy [33].

Olpasiran

Olpasiran is a GalNAc-conjugated siRNA engineered to selectively silence the LPA gene encoding apolipoprotein(a), the defining protein component of lipoprotein(a) . After subcutaneous dosing, the GalNAc moiety binds to ASGPR on hepatocytes, promoting receptor-mediated endocytosis and liver-specific delivery of the siRNA. Within hepatocytes, the siRNA duplex engages the endogenous RNAi pathway: the passenger strand is discarded, while the guide (antisense) strand is incorporated into the RNA-induced silencing complex (RISC) guided by sequence complementarity, RISC binds LPA mRNA in the cytoplasm, and Argonaute proteins within the complex cleave the target transcript [36–39]. The cleaved mRNA fragments are subsequently degraded, preventing apo(a) protein synthesis [38,39]. Because RISC acts catalytically, a single complex can cleave multiple LPA mRNA molecules, resulting in amplified and durable gene silencing [36,38]. The overall consequence is a marked and sustained reduction in apo(a) production and, consequently, profound lowering of circulating Lp(a) levels [36,39]. Clinical data support this mechanism: a phase 1 dose-escalation study demonstrated that a single subcutaneous dose of olpasiran reduced Lp(a) by 71–97% for several months [39]. Furthermore, in the phase 2 OCEAN(a)-DOSE trial, olpasiran administered at doses of 75 mg or higher every 12 weeks achieved reductions exceeding 95%, confirming the potency and durability predicted by its mechanistic profile [36,40].

ApoC-III inhibition for hypertriglyceridemia

Apolipoprotein C-III is a major inhibitor of lipoprotein lipase and promotes persistence of triglyceride-rich lipoproteins. Genetic loss-of-function variants are associated with low triglyceride levels and reduced cardiovascular risk.

Volanesorsen

Volanesorsen (Waylivra®) is an antisense oligonucleotide targeting apolipoprotein C-III (apoC-III) mRNA, developed for the treatment of familial chylomicronemia syndrome (FCS), hypertriglyceridemia, and familial partial lipodystrophy (FPL) [41]. ApoC-III is a 79–amino acid glycoprotein synthesized primarily in the liver and, to a lesser extent, in the intestine. In normolipidemic individuals, apoC-III is predominantly associated with HDL particles, whereas in hypertriglyceridemic states it is largely bound to triglyceride-rich lipoproteins (TRLs). ApoC-III is thought to modulate triglyceride exchange between HDL and TRLs through incompletely understood mechanisms. In addition, apoC-III inhibits lipoprotein lipase activity and impairs hepatic uptake of TRL remnants, indicating its involvement at multiple stages of triglyceride metabolism [42].

Plozasiran

Plozasiran is a GalNAc-conjugated siRNA designed to silence APOC3 mRNA in hepatocytes. Following subcutaneous administration, the GalNAc ligand binds ASGPR on liver cells, enabling efficient and liver-specific uptake. Inside hepatocytes, the siRNA duplex is incorporated into RISC, where the guide strand directs sequence-specific binding to APOC3 mRNA, leading to endonucleolytic cleavage and transcript degradation [43,44].

Olezarsen

Olezarsen is a triantennary GalNAc-conjugated antisense oligonucleotide that lowers apolipoprotein C-III levels and thereby reduces plasma triglycerides by selectively degrading APOC3 mRNA in hepatocytes. After subcutaneous administration, GalNAc-mediated binding to ASGPR facilitates receptor-dependent hepatic uptake, concentrating the drug at .the principal site of apoC-III expression [45,46]. Within hepatocytes, the single-stranded gapmer ASO hybridizes with complementary regions of mature APOC3 mRNA to form an RNA–DNA duplex that is recognized by RNase H1, resulting in cleavage of the RNA strand and transcript degradation. Loss of APOC3 mRNA prevents apoC-III translation and leads to reduced circulating apoC-III concentrations [47].

https://doi.org/10.61577/ijcri.2025.1000020

ANGPTL3-directed therapies

Angiopoietin-like 3 (ANGPTL3) is a hepatocyte-derived inhibitor of lipoprotein lipase and endothelial lipase. Genetic deficiency of ANGPTL3 is associated with low levels of LDL-C and triglycerides and a markedly reduced risk of ASCVD.

Evinacumab

Evinacumab is a recombinant human monoclonal antibody that targets and neutralizes ANGPTL3. Inhibition of ANGPTL3 by evinacumab results in reductions in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. LDL-C lowering occurs independently of LDL receptor function through enhanced processing and clearance of very low-density lipoproteins upstream of LDL formation. Additionally, evinacumab-mediated ANGPTL3 blockade restores lipoprotein lipase and endothelial lipase activity, thereby lowering triglyceride and HDL-C levels, respectively [48].

Vupanorsen

Vupanorsen is a second-generation N-acetylgalactosamine (GalNAc3)-modified antisense oligonucleotide targeting hepatic ANGPTL3 mRNA. GalNAc3 conjugation enables selective delivery to hepatocytes via ASGPR and achieves therapeutic efficacy comparable to unconjugated ASOs at 20- to 30-fold lower doses, thereby reducing systemic exposure [49]. Within hepatocytes, vupanorsen hybridizes to ANGPTL3 mRNA through Watson–Crick base pairing, forming an RNA–DNA duplex that is cleaved by endogenous RNase H1, resulting in degradation of the transcript. Reduced ANGPTL3 expression alleviates inhibition of lipoprotein lipase and endothelial lipase, enhancing intravascular hydrolysis of triglyceride-rich lipoproteins and accelerating remnant clearance. Clinically, this mechanism has been associated with dose-dependent reductions in triglycerides, apolipoprotein C-III, and other atherogenic lipoproteins, as well as non-HDL cholesterol [50].

Targeting Inflammation via RNA Platform

Inflammation is an established driver of atherothrombotic risk: the CANTOS trial demonstrated that selective interleukin-1β blockade with canakinumab reduced major adverse cardiovascular events in patients with prior myocardial infarction and elevated hs-CRP, confirming that modulating discrete inflammatory pathways can lower cardiovascular risk independently of lipid reduction and thereby reinforcing the rationale for targeted anti-inflammatory interventions in cardiometabolic disease [51]. RNA modalities (ASOs, siRNAs and related chemistries) are particularly well aligned with anti-inflammatory drug development because they suppress defined cytokines or inflammasome components at the mRNA level, and advances in chemistry and delivery (GalNAc for hepatocyte targeting, lipid nanoparticles and alternative carriers for extrahepatic tissues, and sugar/backbone modifications to enhance stability and limit innate immune activation) have enabled clinical translation [13]. IL-6 is a compelling RNA target, positioned downstream of NLRP3/IL-1β signaling and central to acute-phase responses, endothelial dysfunction, and chronic vascular inflammation. Preclinical studies show that IL-6 expression can be attenuated by RNAi with protective effects in models of acute lung injury and other inflammatory states, and newer chemically optimized and delivery-enhanced siRNAs (including cholesterol-conjugated and nanoparticle-formulated constructs) further reduce IL-6 output in vitro and in vivo.

The NLRP3 inflammasome functions upstream as a sensor–effector complex regulating IL-1β and IL-18 maturation and sustaining sterile inflammation across cardiovascular, metabolic, and neurodegenerative contexts; both genetic and pharmacologic NLRP3 inhibition mitigate disease features in experimental systems, highlighting its therapeutic relevance. RNA-based strategies directed at NLRP3 include ASOs that suppress transcript abundance or alter splicing. Recent work shows that NLRP3-targeting ASOs decrease inflammasome activation and IL-1β secretion in primary microglia and human macrophage/THP-1 models, while additional groups are advancing ASOs and siRNAs with promising tolerability and target knockdown in rodent and nonhuman primate studies. These findings support the potential for transcript-directed agents to attenuate inflammasome signaling in relevant immune cells.

Important translational considerations persist and are being tackled: (1) cell-specific delivery. Because NLRP3 expression is concentrated in myeloid populations (macrophages, microglia), hepatocyte-targeting GalNAc conjugates are insufficient, necessitating alternative systems (LNPs, ligand- or antibody-mediated targeting, aptamer conjugates, or localized delivery); (2) immunologic consequences of on-target cytokine suppression. Sustained pathway inhibition may affect host defense, requiring careful dose selection and monitoring [13]. RNA therapeutics thus offer a refined set of tools to modulate inflammatory mediators such as IL-6 and NLRP3 at the transcript level; accumulating preclinical data indicate both efficacy and acceptable tolerability (siRNA/ASO-mediated knockdown with reduced cytokine release and disease markers), and future progress hinges on optimizing delivery to immune-lineage cells, managing infection-related risks, and establishing clinical utility in early-phase trials informed by the precedent set by CANTOS.

Limitations and Challenges

RNA-based therapeutics, including ASOs and siRNAs, are emerging as transformative tools in the management of high-risk cardiovascular and metabolic disorders. Patient selection and risk stratification are central to their clinical application. These therapies are most appropriate for patients with genetically determined or refractory lipid abnormalities, such as markedly elevated lipoprotein(a) [Lp(a)], severe hypertriglyceridemia, or mixed dyslipidemia, who have not achieved target levels despite maximal standard-of-care therapy including statins, ezetimibe, and PCSK9 inhibitors. Genetic validation plays an important role, as RNA therapeutics are often designed to silence specific mRNA targets such as LPA, APOC3, or ANGPTL3, making patients with elevated expression of these proteins' ideal candidates. Biomarker-guided therapy is critical, as baseline levels of Lp(a), apoC-III, or ANGPTL3 can not only guide initiation but also monitor therapeutic response [32,47] One of the key advantages of RNA-based therapeutics is their extended duration of action, which allows for infrequent dosing schedules, typically ranging from every few weeks to once every several months. This contrasts with daily oral therapies and may significantly improve adherence, especially in patients managing multiple chronic medications. However, adherence remains essential, as missing a dose may reduce efficacy over time, and structured follow-up with patient education is necessary to ensure persistence of therapy [49]. The safety profile of RNA therapeutics has been favorable in clinical trials. GalNAc-conjugated ASOs and siRNAs are targetedto hepatocytes, minimizing systemic exposure and

https://doi.org/10.61577/ijcri.2025.1000020

immune activation, although mild injection-site reactions are common. Liver function monitoring is recommended due to hepatic uptake, and preclinical studies suggest that chemical modifications to the oligonucleotide backbone reduce the risk of off-target effects and innate immune responses. Long-term surveillance is required to detect any delayed or unforeseen adverse events given the relatively recent introduction of these agents [47,49]. Cost and accessibility remain important practical considerations. The development and manufacturing of RNA therapeutics are resource-intensive, resulting in high projected costs. Initially, access may be restricted to specialty clinics with infusion or injection capabilities, and reimbursement will likely be contingent on patient risk stratification and clinical indication. Health economic analyses, including cost-effectiveness and outcomes-based reimbursement strategies, will be crucial for broader adoption [32]. Finally, integration into current treatment algorithms requires careful consideration. RNA therapeutics are poised to complement existing lipid-lowering and cardiovascular risk management strategies rather than replace them. For instance, Lp(a)-lowering therapies may be added to standard care in patients with residual cardiovascular risk, while apoC-III or ANGPTL3-targeting agents could be used in severe hypertriglyceridemia where conventional therapies are insufficient. Although major guidelines have yet to fully incorporate RNA-based therapies, ongoing phase 3 trials and emerging real-world evidence will inform their eventual place in clinical practice, emphasizing biomarker-guided patient selection, adherence monitoring, and safety surveillance [32,47,49].

Future Direction

The future of RNA-based therapeutics in atherosclerosis is highly promising, driven by the expanding understanding of molecular mechanisms underlying CVD and advances in RNA chemistry, delivery, and safety. Emerging strategies aim to extend beyond conventional lipid-lowering targets to address residual cardiovascular risk, inflammation, and complex metabolic derangements that contribute to atherogenesis. Precision-targeted therapies using ASOs and siRNAs allow for selective silencing of genes implicated in lipid metabolism, such as LPA, APOC3, and ANGPTL3, but also offer the potential to modulate inflammatory pathways central to plaque progression, including interleukin-6 (IL-6) and the NLRP3 inflammasome. Integration of RNA therapeutics with biomarker-guided patient selection is expected to enhance efficacy and safety. Advances in GalNAc-conjugated delivery systems have enabled hepatocyte-specific targeting, which has improved pharmacokinetics, minimized off-target effects, and allowed for infrequent dosing schedules, thereby improving patient adherence and tolerability [32,47]. Beyond hepatocyte- targeted therapies, novel approaches aim to expand tissue-specific delivery to endothelial cells, macrophages, and smooth muscle cells within atherosclerotic plaques, potentially allowing direct modulation of local inflammation and plaque stabilization. Another critical area for future development is RNA-based anti-inflammatory strategies. Early clinical evidence, including the CANTOS trial and exploratory studies of IL-6 and NLRP3 inhibition, demonstrates that targeted suppression of inflammatory mediators can reduce cardiovascular events independently of lipid lowering. RNA therapeutics provide a platform to safely and selectively downregulate these targets, potentially overcoming limitations of biologics such as monoclonal antibodies, including high cost, parenteral delivery, and immunogenicity. Preclinical studies of IL-6 siRNA and cholesterol-modified siRNAs targeting inflammasome components suggest substantial reductions in vascular inflammation and plaque progression, setting the stage for human trials.

Furthermore, combination therapies using RNA therapeutics to simultaneously modulate multiple atherogenic pathways lipid metabolism, inflammation, and thrombosis represent a future direction that may offer synergistic cardiovascular risk reduction. Advances in chemical modifications and nanoparticle or ligand-mediated delivery are expected to enable multiplexed targeting while preserving safety and pharmacodynamic durability.

Conclusion

RNA-based therapeutics represent a promising and rapidly evolving approach for the management of atherosclerosis and cardiovascular disease. Advances in antisense oligonucleotides and small interfering RNA technologies have enabled selective targeting of genes involved in lipid metabolism, inflammation, and plaque progression, offering new opportunities for precision medicine. Future clinical adoption of these therapies will depend on the availability of long-term real-world evidence, cost-effectiveness evaluations, and successful integration into existing guideline-directed treatment strategies. Ongoing phase 3 clinical trials involving Lp(a)-lowering agents, APOC3 inhibitors, and ANGPTL3-targeted therapies are expected to provide important insights regarding patient selection, long-term safety, efficacy, and combination approaches with conventional therapies. In addition, improvements in delivery systems and tissue-specific targeting may further enhance therapeutic outcomes and reduce adverse effects. Overall, RNA-based therapeutics have the potential not only to complement current treatment modalities but also to significantly transform atherosclerosis management and address residual cardiovascular risk in patients despite standard care.

Disclosure Statement

No potential conflict of interest was reported by the author.

References

1. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of atherosclerosis. Int J Mol Sci. 2022;23(6):3346. https://doi.org/10.3390/ijms23063346
2. Frostegård JS. SLE, atherosclerosis and cardiovascular disease. J Intern Med. 2005;257(6):485-495. https://doi.org/10.1111/j.1365-2796.2005.01502.x
3. Barquera S, Pedroza-Tobías A, Medina C, Hernández-Barrera L, Bibbins-Domingo K, Lozano R, et al. Global overview of the epidemiology of atherosclerotic cardiovascular disease. Arch Med Res. 2015;46(5):328-338.
4. Yang L, Zheng B, Gong Y. Global, regional and national burden of ischemic heart disease and its attributable risk factors from 1990 to 2021: a systematic analysis of the Global Burden of Disease study 2021. BMC Cardiovasc Disord. 2025;25(1):625. https://doi.org/10.1186/s12872-025-05022-x
5. Di Cesare M, Bixby H, Gaziano T, Hadeed L, Kabudula C, McGhie DV, et al. World heart report 2023: Confronting the world's number one killer. World Heart Federation: Geneva, Switzerland. 2023;1.
6. Jia X, Lorenz P, Ballantyne CM. Poststatin lipid therapeutics: A review. Methodist Debakey Cardiovasc J.. 2019;15(1):32. https://doi.org/10.14797/mdcj-15-1-32

https://doi.org/10.61577/ijcri.2025.1000020

7. Lamia TH, Shah-Riar P, Khanam M, Khair F, Sadat A, Tania MK, et al. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors as adjunct therapy to statins: a new frontier in cardiovascular risk reduction. Cureus. 2024;16(10):e71365. https://doi.org/10.7759/cureus.71365
8. Burnett JC, Rossi JJ. RNA-based therapeutics: current progress and future prospects. Chemistry & biology. 2012;19(1):60-71. https://doi.org/10.1016/j.chembiol.2011.12.008
9. Schoenmaker L, Witzigmann D, Kulkarni JA, Verbeke R, Kersten G, Jiskoot W, et al. mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability. Int J Pharm. 2021;601:120586.
10. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):11-21. https://doi.org/10.1056/NEJMoa1716153
11. Edinoff AN, Nguyen LH, Odisho AS, Maxey BS, Pruitt JW, Girma B, et al. The antisense oligonucleotide nusinersen for treatment of spinal muscular atrophy. Orthop Rev. 2021;13(2):24934. https://doi.org/10.52965/001c.24934
12. Booth BJ, Nourreddine S, Katrekar D, Savva Y, Bose D, Long TJ, et al. RNA editing: Expanding the potential of RNA therapeutics. Mol Ther. 2023;31(6):1533-1549. https://doi.org/10.1016/j.ymthe.2023.01.005
13. Zhu Y, Zhu L, Wang X, Jin H. RNA-based therapeutics: an overview and prospectus. Cell death & disease. 2022;13(7):644. https://doi.org/10.1038/s41419-022-05075-2
14. Bajan S, Hutvagner G. RNA-based therapeutics: from antisense oligonucleotides to miRNAs. Cells. 2020;9(1):137. https://doi.org/10.3390/cells9010137
15. Corydon IJ, Fabian-Jessing BK, Jakobsen TS, Jørgensen AC, Jensen EG, Askou AL, et al. 25 years of maturation: A systematic review of RNAi in the clinic. Mol Ther Nucleic Acids. 2023;33:469-482. https://doi.org/10.1016/j.omtn.2023.07.018
16. Zhang J, Chen B, Gan C, Sun H, Zhang J, Feng L. A comprehensive review of small interfering RNAs (siRNAs): mechanism, therapeutic targets, and delivery strategies for cancer therapy. Int J Nanomed. 2023:7605-7635. https://doi.org/10.2147/IJN.S436038
17. Bajan S, Hutvagner G. RNA-based therapeutics: from antisense oligonucleotides to miRNAs. Cells. 2020;9(1):137. https://doi.org/10.3390/cells9010137
18. Qin S, Tang X, Chen Y, Chen K, Fan N, Xiao W, et al. mRNA-based therapeutics: powerful and versatile tools to combat diseases. Signal Transduct Target Ther. 2022;7(1):166. https://doi.org/10.1038/s41392-022-01007-w
19. Kowalski PS, Rudra A, Miao L, Anderson DG. Delivering the messenger: advances in technologies for therapeutic mRNA delivery. Molecular Ther. 2019;27(4):710-728. https://doi.org/10.1016/j.ymthe.2019.02.012
20. Debacker AJ, Voutila J, Catley M, Blakey D, Habib N. Delivery of oligonucleotides to the liver with GalNAc: from research to registered therapeutic drug. Molecular Ther. 2020;28(8):1759-1771. https://doi.org/10.1016/j.ymthe.2020.06.015
21. Zhang Y, Liu H, Zhen W, Jiang T, Cui J. Advancement of drugs conjugated with GalNAc in the targeted delivery to hepatocytes based on asialoglycoprotein receptor. Carbohydr Res. 2025;552:109426.
22. An G. Pharmacokinetics and pharmacodynamics of GalNAc-Conjugated siRNAs. Carbohydr Res. 2024;64(1):45-57. https://doi.org/10.1002/jcph.2337
23. Liu Y, Ou Y, Hou L. Advances in RNA-based therapeutics: Challenges and innovations in RNA delivery systems. Curr Issues Mol Biol. 2024;47(1):22. https://doi.org/10.3390/cimb47010022
24. Lamb YN. Inclisiran: first approval. Drugs. 2021;81(3):389. https://doi.org/10.1007/s40265-021-01473-6
25. Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med. 2017;376(15):1430-1440. https://doi.org/10.1056/NEJMoa1615758
26. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. https://doi.org/10.1056/NEJMoa1912387
27. NOVARTIS F. Approves Novartis Leqvio®(inclisiran), First-in-Class siRNA to Lower Cholesterol and Keep It Low with Two Doses a Year [Internet].
28. Naoum I, Saliba W, Aker A, Zafrir B. Lipid-lowering therapy with inclisiran in the real-world setting: Initial data from a national health care service. J Clin Lipidol. 2024;18(5):e809-e816.
29. Bhatia HS, Bajaj A, Goonewardena SN, Moriarty PM. Pelacarsen: Mechanism of action and Lp (a)-lowering effect. J Clin Lipidol. 2025.
30. Cho L, Nicholls SJ, Nordestgaard BG, Landmesser U, Tsimikas S, Blaha MJ, et al. Design and rationale of Lp(a) HORIZON trial: assessing the effect of lipoprotein(a) lowering with pelacarsen on major cardiovascular events in patients with CVD and elevated Lp(a). Am Heart J. 2025;287:1-9.
31. Ramírez-Cortés F, Ménová P. Hepatocyte targeting via the asialoglycoprotein receptor. RSC Med Chem. 2025;16(2):525-544. https://doi.org/10.1039/D4MD00652F
32. Collotta D, Bertocchi I, Chiapello E, Collino M. Antisense oligonucleotides: a novel Frontier in pharmacological strategy. Front Pharmacol. 2023;14:1304342. https://doi.org/10.3389/fphar.2023.1304342
33. Passey S, Jha J, Chanda A, Pillai A, Frishman WH, Aronow WS. Advances in RNA-Based Therapies Targeted at Lipoprotein (a): Olpasiran in the Management of Atherosclerotic Cardiovascular Disease. Cardiol Rev. 2025:10-97. https://doi.org/10.1097/CRD.0000000000001017
34. Sarzani R, Spannella F, Di Pentima C, Giulietti F, Landolfo M, Allevi M. Molecular therapies in cardiovascular diseases: small interfering RNA in atherosclerosis, heart failure, and hypertension. Int J Mol Sci. 2023;25(1):328. https://doi.org/10.3390/ijms25010328
35. Koren MJ, Moriarty PM, Baum SJ, Neutel J, Hernandez-Illas M, Weintraub HS, et al. Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). Nat Med. 2022;28(1):96-103. https://doi.org/10.1038/s41591-021-01634-w
36. Almaadawy O, Hesn MM, Elsalamony YA, Abobakr OA, Elshimy AH, Abulkhair KA, et al. Small interfering RNA effect on lipoprotein(a). a systematic review. Egypt Heart J. 2025;77(1):44. https://doi.org/10.1186/s43044-025-00635-1
37. Paik J, Duggan S. Volanesorsen: First Global Approval: J. Paik, S. Duggan. Drugs. 2019;79(12):1349-1354. https://doi.org/10.1007/s40265-019-01168-z
38. Calcaterra I, Lupoli R, Di Minno A, Di Minno MN. Volanesorsen to treat severe hypertriglyceridaemia: A pooled analysis of randomized controlled trials. Eur J Clin Investig. 2022;52(11):e13841. https://doi.org/10.1111/eci.13841

https://doi.org/10.61577/ijcri.2025.1000020

39. Gaudet D, Pall D, Watts GF, Nicholls SJ, Rosenson RS, Modesto K, et al. Plozasiran (ARO-APOC3) for severe hypertriglyceridemia: the SHASTA-2 randomized clinical trial. JAMA Cardiology. 2024;9(7):620-630. https://doi.org/10.1001/jamacardio.2024.0959
40. Biessen EA, Van Berkel TJ. N-acetyl galactosamine targeting: paving the way for clinical application of nucleotide medicines in cardiovascular diseases. Arterioscler Thromb Vasc Biol. 2021;41(12):2855-2865. https://doi.org/10.1161/ATVBAHA.121.316290
41. Karwatowska-Prokopczuk E, Lesogor A, Yan JH, Hoenlinger A, Margolskee A, Li L, et al. Efficacy and safety of olezarsen in lowering apolipoprotein C-III and triglycerides in healthy Japanese Americans. Lipids Health Dis. 2024;23(1):329. https://doi.org/10.1186/s12944-024-02297-5
42. Dingman R, Bihorel S, Gusarova V, Mendell J, Pordy R. Evinacumab: Mechanism of action, clinical, and translational science. Clin Transl Sci. 2024;17(6):e13836. https://doi.org/10.1111/cts.13836
43. Gaudet D, Karwatowska-Prokopczuk E, Baum SJ, Hurh E, Kingsbury J, Bartlett VJ, et al. Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia. Eur Heart J. 2020;41(40):3936-3945. https://doi.org/10.1093/eurheartj/ehaa689
44. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119-1131. https://doi.org/10.1056/NEJMoa1707914
45. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. The Lancet. 2017;390(10105):1833-1842. https://doi.org/10.1016/S0140-6736(17)32247-X
46. Crooke ST, Witztum JL, Bennett CF, Baker BF. RNA-targeted therapeutics. Cell Metab. 2018;27(4):714-739. https://doi.org/10.1016/j.cmet.2018.03.004
47. Xu B, Yu DM, Liu FS. Effect of siRNA-induced inhibition of IL-6 expression in rat cerebral gliocytes on cerebral edema following traumatic brain injury. Mol Med Rep. 2014;10(4):1863-1868. https://doi.org/10.3892/mmr.2014.2462
48. Chernikov IV, Bachkova IK, Sen'kova AV, Meschaninova MI, Savin IA, Vlassov VV, et al. Cholesterol-modified anti-il6 siRNA reduces the severity of acute lung injury in mice. Cells. 2024;13(9):767. https://doi.org/10.3390/cells13090767
49. Blevins HM, Xu Y, Biby S, Zhang S. The NLRP3 inflammasome pathway: a review of mechanisms and inhibitors for the treatment of inflammatory diseases. Front Aging Neurosci. 2022;14:879021. https://doi.org/10.3389/fnagi.2022.879021
50. Braatz C, Komes MP, Ravichandran KA, de Fragas MG, Griep A, Schwartz S, et al. NLRP3-directed antisense oligonucleotides reduce microglial immunoactivities in vitro. J Neurochem. 2024;168(10):3467-3481. https://doi.org/10.1111/jnc.15778
51. Crooke ST, Witztum JL, Bennett CF, Baker BF. RNA-targeted therapeutics. Cell Metab. 2018;27(4):714-739. https://doi.org/10.1016/j.cmet.2018.03.004

https://doi.org/10.61577/ijcri.2025.1000020