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REVIEW

# RNA interference therapy in cardiology: will new targets improve therapeutic goals?

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## Abstract

The discovery of RNA interference in 1998 opened avenues for the manipulation of gene expression, leading to the development of small interfering RNA (siRNA) drugs. Patisiran, the first FDA-approved siRNA medication, targets hereditary transthyretin amyloidosis with polyneuropathy. Givosiran, lumasiran and nedosiran further expand siRNA applications in treating rare genetic diseases, demonstrating positive outcomes. In cardiology, inclisiran, approved for hypercholesterolaemia, showcases sustained reductions in LDL cholesterol levels. However, ongoing research aims to establish its impact on cardiovascular outcomes. Lipoprotein(a), an independent risk factor for atherosclerotic cardiovascular disease, has become a focus of siRNA therapies, precipitating the development of specific siRNA drugs like olpasiran, zerlasiran and lepodisiran, with promising reductions in lipoprotein(a) levels. Research to assess the effectiveness of these medications in reducing events is currently under way. Zodasiran and plozasiran address potential risk factors for cardiovascular diseases, targeting triglyceride-rich lipoproteins. Zilebesiran, which targets hepatic angiotensinogen mRNA, has demonstrated a dose-related reduction in serum angiotensinogen levels, thereby lowering blood pressure in patients with systemic arterial hypertension. The evolving siRNA methodology presents a promising future in cardiology, with ongoing studies assessing its effectiveness in various conditions. In the future, larger studies will provide insights into improvements in cardiovascular outcomes, long-term safety and broader applications in the general population. This review highlights the historical timeline of the development of siRNA-based drugs, their clinical indications, potential side-effects and future perspectives.

**Keywords:** dyslipidaemia, small interfering RNA, systemic arterial hypertension.

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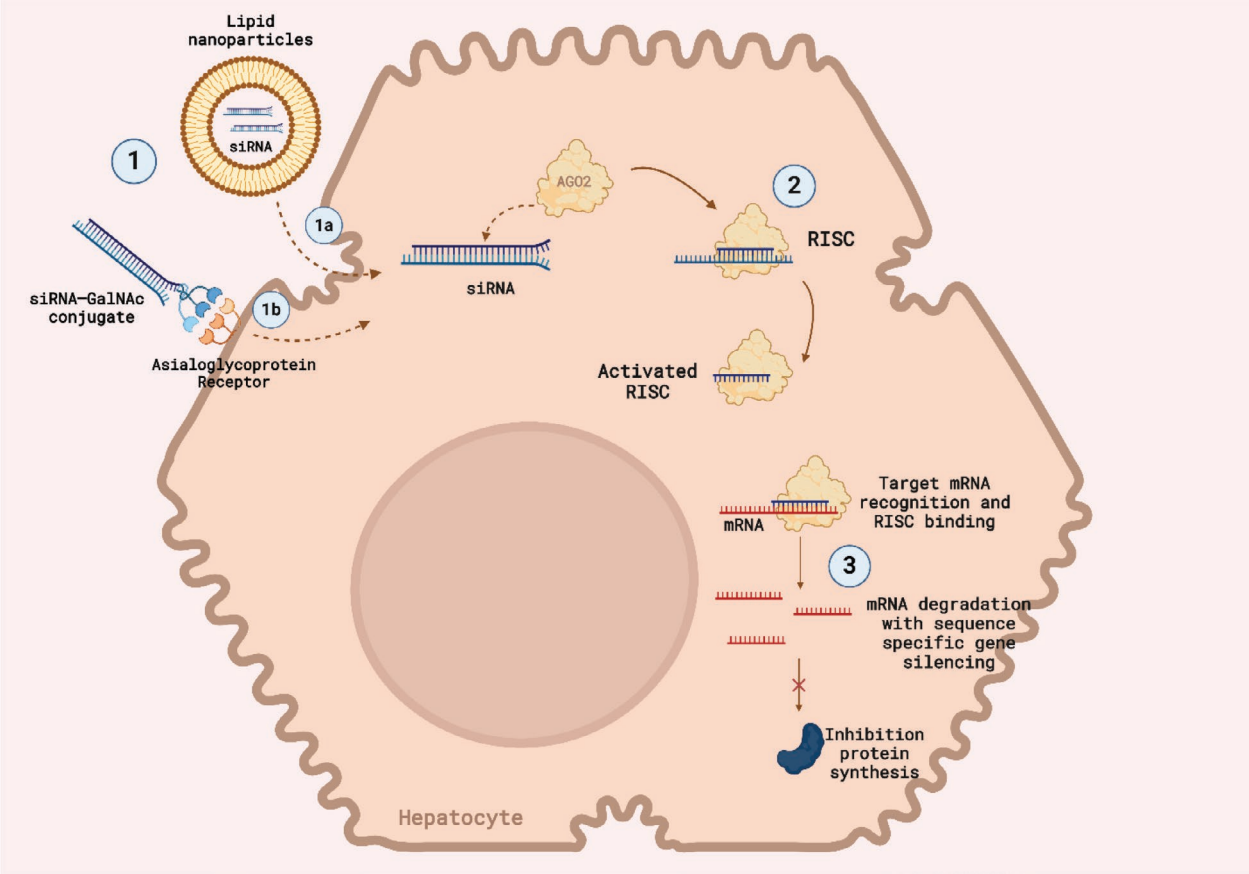
# Introduction

The understanding of RNA as a fundamental part of genetic information sequencing was reported by Crick in 1958.[1] Since then, several research groups have focused on the study of RNA, developing the theoretical foundation that enables its clinical applicability in modern medicine.[2] In 1978, Zamecnik and Stephenson provided the first description of medications capable of modulating gene expression, demonstrating that an antisense oligonucleotide could inhibit the viral replication of Rous sarcoma virus in culture.[3] Formerly, antisense oligonucleotides were small single-stranded molecules that could alter RNA and modify protein expression through various distinct mechanisms. However, their performance in the first generation of drugs was not as desired as they have restricted passive diffusion into the cell and are susceptible to degradation.[4,5] In 1998, RNA interference, a double-stranded RNA that constitutes a natural defence mechanism in eukaryotic species capable of suppressing expression of a target protein by initiating degradation of the corresponding mRNA, was first reported (Figure 1).[6,7] Twenty years later, the FDA approved the first small interfering RNA (siRNA) drug, patisiran (Figure 2). Such medications aim to manipulate gene expression, causing suppression of the target gene, as they duplicate together with RNA interference, introducing the RNA-induced silencing complex, thereby preventing the transcription of mRNA.[8,9] The process of developing medications using this technology is complex; however, once the chemical composition of

**Figure 1. Mechanism of action of small interference (siRNA) molecules. 1 – siRNA delivery methods in hepatocytes: (a) lipid nanoparticles enter the cell by endocytosis, releasing siRNA cargo into the cytosol. (b) Conjugated N-acetylgalactosamine (GalNAc) binds to asialoglycoprotein receptor expressed on hepatocyte membrane; the complex undergoes a process of internalization in lysosomes with subsequent release of its siRNA cargo. 2 – siRNA associates with Argonaute2 (Ago2) enzyme to form the RNA-induced silencing complex (RISC), being cleaved into a single strand and becoming active. 3 – The strand within the complex serves as a guide for the enzyme to cleave the target region in the messenger RNA (mRNA), silencing its effect.**




RNA and the methods of delivering to the target organ are known, it becomes feasible to swiftly create and synthesize new medications.[2,10] This review highlights the historical timeline of the development of siRNA-based drugs, their clinical indications, introduction into cardiology research and practice, potential side-effects, and future perspectives.

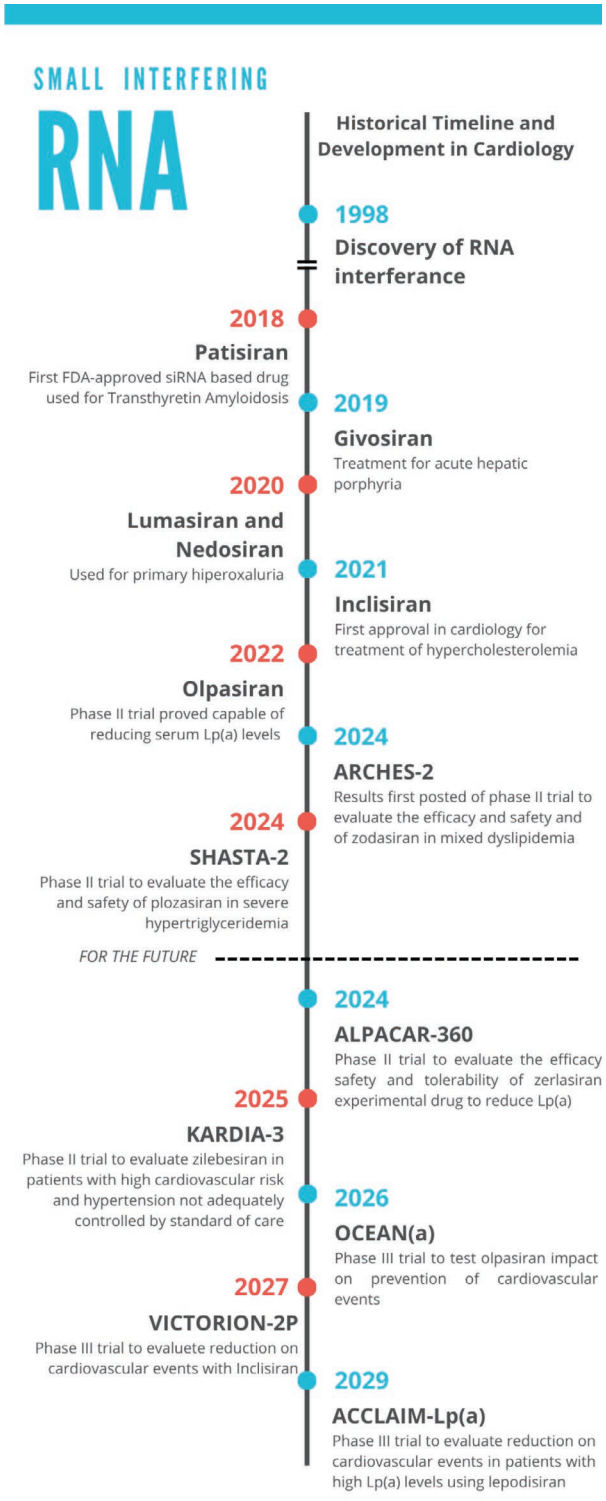
# Methods

We conducted a literature search on PubMed and Google Scholar using the following keywords searched alone and in interactive combinations: "RNA interference", "small interfering RNA drug", "amyloidosis", "acute hepatic porphyria", "hypercholesterolemia", "hypertension", "lipoprotein(a)" and "cardiovascular risk". For each drug mentioned in the article, we carried out extensive research on ClinicalTrials.org about finished and ongoing trials and their respective references. The search strategy included clinical trials, observational studies, meta-analyses, guidelines, reviews and cross-references of the relevant articles.

# Review

Patisiran was the first siRNA drug to be released and commercialized, with its use indicated in patients with hereditary transthyretin amyloidosis (ATTR) with polyneuropathy.[11] The medication consists of a siRNA molecule with a delivery system based on lipid nanoparticles that bind to apolipoprotein E (ApoE) and enter hepatocytes through ApoE receptors. Subsequently, patisiran binds to mRNA, suppressing the transcription of transthyretin (TTR) protein and its deposition.[2] Patisiran was validated in the APOLLO study, which showed significant improvement in specific clinical scores for neuropathy compared to

**Figure 2. Historical timeline of development of siRNA-based drugs.**




placebo as well as a reduction in serum TTR protein levels by about 81%.[12] Currently, a multicentre observational, phase IV study is under way to assess the effectiveness of patisiran in large-scale use, although its use is recommended in specific guidelines as a disease-modifying therapy option for those with pure polyneuropathy, with the level of evidence II and grade for recommendation A.[13,14] Pre-specified sub-group analyses from the APOLLO study suggested potential benefits of the medication in patients with cardiac involvement, halting the progression of manifestations; however, studies designed for this purpose were necessary for the approval of use in this scenario.[15] In a recent publication, the APOLLO-B trial tested patisiran in patients with ATTR cardiomyopathy to assess its effect on functional capacity, evaluated through the distance covered in the 6-minute walk test, with significantly less decline from baseline observed in those who received the medication.[16]

A few years after the approval of the first medication, givosiran emerged as a siRNA delivered via conjugated N-acetylgalactosamine (GalNAc), with the possibility of subcutaneous administration. Givosiran is indicated for the treatment of acute hepatic porphyria, targeting the reduction of aminolevulinate synthase 1 enzyme production, leading to a consequent reduction in the production and accumulation of neurotoxic metabolites.[6] Givosiran led to a 74% lower rate of porphyria attacks during the 6-month intervention period compared to controls.[17] Following 36 months of medication use, extended-term analyses revealed consistent outcomes, and there were no safety concerns that emerged.[18] Similar treatments for rare genetic diseases were then investigated, including lumasiran and nedosiran for primary hyperoxaluria, currently incorporated into the guidelines as an option for those who have not responded to traditional treatment with pyridoxine.[19] The first to be studied was lumasiran; in a phase III trial, lumasiran demonstrated a reduction in urinary oxalate excretion after 6 months of treatment to levels near normal, with effects already evident in the first month and sustained after long-term use analysis at 12 months. The drug maintained a favourable safety profile, with the majority of adverse effects correlated to the drug application site.[20,21] Following suit, nedosiran was tested using the same rationale and yielded positive results in reducing urinary oxalate excretion in children and adults with primary hyperoxaluria type 1 and 2 after 6 months of treatment.[22]

Under the scope of cardiology, this technique gained strength with the development of inclisiran, approved by the FDA for hypercholesterolaemia in 2021, becoming the first time a siRNA drug was indicated for a highly prevalent disease.[2,6] Inclisiran is delivered via GalNAc, targeting the suppression of proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis in the liver, responsible for LDL receptor endocytosis and degradation. Its inhibition increases receptor renewal and availability, leading to the sustained reduction of circulating LDL.[2,11] In the phase II trial ORION-1, multiple doses and dosing intervals were tested in patients at high

cardiovascular risk who had high LDL cholesterol levels despite being on maximum-tolerated statin therapy.[23] At the end of the study, the most significant decrease in LDL cholesterol levels was noted when using two yearly doses of 300 mg, with a reduction of 52.6% from baseline at day 240.[24] The ORION-3 was an extension study of ORION-1 aimed at evaluating long-term efficacy and safety of twice-yearly inclisiran administration, and showed a 44.2% reduction over a period of 4 years, with no new safety concerns identified.[24]

Subsequently, the phase III studies ORION-10 and ORION-11 assessed the use of inclisiran in patients with atherosclerotic cardiovascular disease and those with equivalent risk (type 2 diabetes, familial hypercholesterolaemia or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease), demonstrating a percentage change in LDL cholesterol level at day 510 of −51.3% in ORION-10 and −45.8% in ORION-11 with inclisiran administered subcutaneously every 6 months.[25] However, despite the significant reductions in LDL serum levels, research studies that aim to show a reduction in cardiovascular events or progression of disease due to the medication are essential and are presently in progress. Examples include VICTORION-1 PREVENT and VICTORION-2 PREVENT, which will assess the reduction of major cardiovascular outcomes, defined as composite of cardiovascular death, non-fatal myocardial infarction and non-fatal ischaemic stroke, compared to placebo associated with high-intensity statin therapy.[26,27] Also in progress is the VICTORION-PLAQUE study, which aims to evaluate the reduction of total coronary atheroma volume assessed by coronary computed tomography angiography in patients with non-obstructive lesions and without previous cardiovascular events after receiving inclisiran at 300 mg on day 1, once at 3 months, and once every 6 months up until month 21.[28]

Lipoprotein(a) (Lp(a)) is a particle composed of LDL covalently bound to apolipoprotein(a), with its serum levels primarily influenced by genetic determination. Currently, it is known that elevated serum levels of Lp(a) (>50 mg/dL) are an independent risk factor for atherosclerotic cardiovascular disease (ASCVD). However, whilst the reduction of LDL levels has a well-defined role in cardiovascular disease prevention, it is uncertain whether its reduction of LP(a) impacts the decrease of cardiovascular events, and what patient profile would benefit from this measure. Although current evidence shows a partial reduction in Lp(a) levels with the use of statins and PCSK9 inhibitors, the development of a specific drug for this purpose has been the focus of major studies.[29] Olpasiran is a siRNA molecule administered subcutaneously and delivered to the liver through the GalNAc system, where it binds to apolipoprotein(a) mRNA, inducing its degradation. The phase II OCEAN(a)-DOSE study, published in November 2022, demonstrated that olpasiran is capable of reducing serum Lp(a) levels by over 95% when administered every 12 weeks at doses of 75 mg or 225 mg, with a favourable safety profile.[30] Currently, a phase III study is active and testing the impact of the medication on the prevention of major cardiovascular events, defined as heart disease death, myocardial infarction or urgent coronary revascularization, in patients with ASCVD and elevated Lp(a) levels compared to placebo.[31]

Following the same purpose of reducing circulating Lp(a) levels, two new drugs are being studied: zerlasiran and lepodisiran. The experimental drug SLN360, also known as zerlasiran, demonstrated in its phase I study a reduction in serum Lp(a) levels of up to 96–98% after receiving doses of 300 mg and 600 mg. The reduction was sustained at 71–81% even after 5 months compared to baseline.[32] A new phase II trial, ALPACAR-360, aims to demonstrate the safety and tolerability of the medication in adults with isolated elevated Lp(a) levels or in association with a high risk for the development of ASCVD events[33,34]. At the same time, lepodisiran, a siRNA drug targeting the inhibition of hepatic synthesis of apolipoprotein(a), was tested in a population of 48 volunteers without cardiovascular disease presenting serum concentrations of Lp(a) above 75 nmol/L, aiming to evaluate the safety, tolerability and effect of the drug at ascending doses.[35] This phase I trial evidenced that plasma concentrations of lepodisiran reached their peak levels at an average of 10.5 hours, and became undetectable at 48 hours post administration. Doses of 4, 12, 32, 96, 305 and 608 mg were tested, with the maximum median reduction in Lp(a) concentration of 94% observed after 48 weeks compared to baseline in the group receiving the 608 mg dose, maintaining a favourable safety profile with mild and transient adverse effects such as headache.[36] At present, the ACCLAIM-Lp(a), phase III, randomized and double-blind study is undergoing recruitment. Its primary objective is to evaluate the effectiveness of a new treatment in reducing the risk of cardiovascular events compared to a placebo amongst individuals with Lp(a) levels equal to or exceeding 175 nmol/L, who either have established cardiovascular disease or are at high risk of experiencing their first cardiovascular event.[36]

In the same way as Lp(a), triglyceride-rich lipoproteins (TRLs) should be cited as new therapeutic targets directed at cardiovascular risk reduction. TRLs constitute a heterogeneous group comprised of chylomicrons bound to apolipoproteins (Apo)C-II, ApoC-III and ApoE. Recent studies suggest that these lipoproteins may potentially contribute to endothelial inflammation, which could result in an increased risk of cardiovascular

events.[37] In this scenario, two potential drugs have arisen and are currently undergoing trials: zodasiran (ARO-ANG3) and plozasiran (ARO-APOC3).

The first of these, zodasiran, targets angiopoietin-like protein 3 (ANGPTL3), a key regulator of circulating triglyceride (TG) and TRL levels as well as cholesterol levels. In its phase I study, it demonstrated a reduction of 92.7% in serum concentrations of ANGPTL3 as well as in serum levels of TG and atherogenic lipoproteins.[38] The phase II ARCHES-2 trial primary outcome was to evaluate the percentage variation in plasma TG levels over 24 weeks, following quarterly administration of the medication at three doses (50, 100 or 200 mg) in patients with mixed hyperlipidaemia. Treatment with zodasiran was associated with a dose-dependent reduction in TG levels, reaching −63% with 200 mg. The study also assessed variations in ANGPTL3, LDL cholesterol and apolipoprotein B levels over the same 24 weeks, achieving a reduction of 74%, 20% and 22%, respectively. A concern regarding its usage pertains to the worsening of glycaemic control in patients with diabetes, evidenced by an increase in glycosylated haemoglobin levels within this population.[39]

The second drug, plozasiran, is designed to suppress the expression of ApoC-III, consequently reducing TG levels. A phase I study primarily aimed to assess the drug's safety profile and found an emerging adverse effect of transient and asymptomatic elevation of liver transaminases to mild to moderate levels; amongst its secondary objectives, in the hypertriglyceridaemia cohorts, a reduction of up to 94.4% in serum ApoC-III levels and 81% in TG levels was observed with the same dosage of 100 mg.[40] In the SHASTA-2 trial, a phase II study, the same drug was assessed in patients with severe hypertriglyceridaemia, with the primary outcome being the percentage change in serum TG levels over 24 weeks. The mean baseline TG level in this study was 897 mg/dL, showing a reduction of 57% after two doses of 50 mg, with 90.6% of patients achieving TG levels below 500 mg/dL.[41] Another phase II study investigated plozasiran in the context of mixed hyperlipidaemia, resulting in a −62.4% variation in plasma TG levels with the 50-mg-quarterly dose. Regarding safety outcomes, there was no significant change in mean platelet count or aminotransferase levels compared to placebo.[42] Phase III studies are ongoing, and research on the reduction of cardiovascular outcomes due to medication use still needs to be conducted.

Other cardiovascular risk factors have also been the subject of study as a possibility for new therapeutic targets as demonstrated by the recently published phase I trial on zilebesiran focusing on the treatment of systemic arterial hypertension. This involves a siRNA molecule also delivered to the liver via the GalNAc system, which targets the specific reduction of hepatic angiotensinogen mRNA, consequently reducing angiotensinogen production. Moreover, the same study observed a dose-related reduction of up to 90% in serum angiotensinogen levels, which led to blood pressure reduction. This result was achieved after a single dose of the medication, which was sustained for up to 24 weeks. The most common side-effect was a transient injection site reaction. No hypotension, hyperkalaemia or renal function worsening was observed.[43] However, despite the safety profile demonstrated by the study, concerns have been raised about scenarios, such as shock and hypovolaemia, in which the renin–angiotensin system must be activated quickly. Considering this, simultaneous development has taken place with a platform called REVERSIR, which aims to reverse siRNA activity.[44,45] Other strategies that have been tested to reverse the effect of the medication in emergencies include the use of vasopressors, saline solution and fludrocortisone.[46] Currently, two phase II trials, KARDIA-1 and KARDIA-2, are under way to demonstrate the efficacy and safety of zilebesiran in patients with mild-to-moderate hypertension without prior therapy and in those with uncontrolled hypertension by a standard-of-care antihypertensive medication, respectively.[47,48] At the same time, KARDIA-3, also a phase II trial and currently recruiting patients, aims to study the effects of the medication in combination with established antihypertensive medications in patients with an unmet target.[49]

The growing development of gene-modifying therapies in cardiology has expanded the scope of research, leading to the discovery of additional genome-editing tools. One such example is found in the recent VERVE studies, which employ adenine base editor methodology, enabling the precise cleavage of DNA at specific positions through adenine-to-guanine substitutions, thereby resulting in the silencing of targeted gene expression.[50] Ongoing research endeavours aim to evaluate two products designed for the permanent silencing of the PCSK9 gene, and one targeting the ANGPTL3 gene. These studies focus on patients with heterozygous familial hypercholesterolaemia, with the overarching goal of assessing cardiovascular risk reduction.[51–53]

# Conclusion

The perspective for the use of siRNA methodology is increasing in medicine and has a promising future in cardiology as a growing array of medications are being tested for several conditions (Table 1), including less common disorders, like ATTR amyloidosis, or more common clinical conditions, like dyslipidaemia and hypertension, both of which are independent risk factors for the development of cardiovascular disease. Its potential for

**Table 1. Small interfering RNA (siRNA)-based drugs and corresponding clinical trials.**

| Drug | Condition | Delivery system | Target | Phase, status | NCT ID |
|---|---|---|---|---|---|
| Patisiran | Transthyretin amyloidosis | Lipid nanoparticles | Hereditary transthyretin | III, completed | NCT04201418<br>NCT03862807<br>NCT01617967<br>NCT02510261<br>NCT01961921<br>NCT01960348<br>NCT02053454<br>NCT01559077 |
| Givosiran | Acute hepatic porphyria | GalNAc–siRNA conjugate | ALAS1 | III, completed | NCT03338816<br>NCT02949830<br>NCT03505853<br>NCT02452372 |
| Lumasiran | Primary hyperoxaluria type 1 | GalNAc–siRNA conjugate | HAO1 | III, active, not recruiting<br>II, completed | NCT04152200<br>NCT03905694<br>NCT03681184<br>NCT03350451<br>NCT02706886 |
| Nedosiran | Primary hyperoxaluria | GalNAc–siRNA conjugate | Hepatic LDH | III, enrolling by invitation<br>II, completed | NCT04042402<br>NCT03847909<br>NCT04555486 |
| Inclisiran | Hypercholesterolaemia | GalNAc–siRNA conjugate | PCSK9 | IV, active not recruiting, recruiting or not yet recruiting<br>III, completed, active, not recruiting or recruiting | NCT05192941<br>NCT05834673<br>NCT06280976<br>NCT06386419<br>NCT06249165<br>NCT06421363<br>NCT06338293<br>NCT06431763<br>NCT06372925<br>NCT04929249<br>NCT03814187<br>NCT03397121<br>NCT03851705<br>NCT03400800<br>NCT03399370<br>NCT04807400<br>NCT04873934<br>NCT05888103<br>NCT04652726<br>NCT04659863<br>NCT03705234<br>NCT05004675<br>NCT04765657<br>NCT05763875<br>NCT05030428<br>NCT05682378<br>NCT05360446<br>NCT05739383 |

(*Continued*)

**Table 1. (Continued)**

| Drug | Condition | Delivery system | Target | Phase, status | NCT ID |
|---|---|---|---|---|---|
| Olpasiran | Cardiovascular disease | GalNAc–siRNA conjugate | Lp(a) | III, active, not recruiting<br>II, completed | NCT05581303<br>NCT04270760<br>NCT04987320<br>NCT05481411 |
| Zilebesiran | Hypertension | GalNAc–siRNA conjugate | AGT | II, active, not recruiting, recruiting or not yet recruiting<br>I, completed | NCT05103332<br>NCT04936035<br>NCT06272487<br>NCT06423352<br>NCT03934307 |
| Zerlasiran (SLN 360) | Elevated Lp(a) | GalNAc–siRNA conjugate | Lp(a) | II, active, not recruiting<br>I, completed | NCT05537571<br>NCT04606602 |
| Lepodisiran | Elevated Lp(a) | GalNAc–siRNA conjugate | Apolipoprotein(a) | III, recruiting | NCT06292013 |
| Zodasiran (ARO-ANG3) | Dyslipidaemia and homozygous familial hypercholesterolemia | GalNAc–siRNA conjugate | ANGPTL3 | II, active, not recruiting<br>I, completed | NCT04832971<br>NCT04832971<br>NCT05217667<br>NCT03747224 |
| Plozasiran (ARO-APOC3) | Dyslipidaemia, severe hypertriglyceridaemia and familial chylomicronaemia syndrome | GalNAc–siRNA conjugate | ApoC-III | III, not yet recruiting or active, not recruiting<br>II, completed<br>I, completed | NCT05902598<br>NCT06347133<br>NCT06347003<br>NCT05413135<br>NCT05089084<br>NCT04720534<br>NCT04998201<br>NCT03783377 |

ANGPTL3, angiopoietin-like protein 3; ApoC, apolipoprotein C; GalNAc, N-acetylgalactosamine; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9.

long-term effects and having an option of periodic applications instead of daily continuous use translate into a greater possibility of effectiveness and good adherence to therapy. On the other hand, concerns regarding the stability of delivery systems and the specificity of the target to be achieved to prevent non-specific off-target effects must be considered. Although the general safety profile in patients showed promising results during phase I and II trials of multiple medications, some studies observed transient elevations in liver transaminases, despite their asymptomatic nature. These increases may potentially be linked to off-target effects facilitated by the GalNAc–siRNA conjugate. Based on these observations, studies utilizing in vitro and in vivo data in rats are currently under way, aiming to enhance the stability of these medications.[54] Additionally, long-term monitoring of potential side-effects is crucial given that this technology has recently been incorporated into humans. In the early future, larger studies will provide us answers regarding improvements in cardiovascular outcomes as well as the long-term safety and broad use in the general population.

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