



GALNAC-CONJUGATED SIRNA THERAPEUTICS IN CARDIOVASCULAR MEDICINE: PHARMACEUTICAL BASIS, CLINICAL EVIDENCE AND ACCESS IN INDIA

Pharmaceutical Science

Sonalin Rout*

Lecturer, KIIT School of Pharmacy, KIIT Deemed to be University, Bhubaneswar, Odisha 751024, India. *Corresponding Author

Dr. Raghvendra Shridhar

Senior Resident, Department of Cardiology, Kalinga Institute of Medical Sciences, KIIT Deemed to be University, Bhubaneswar, Odisha 751024, India

ABSTRACT

Small interfering RNA (siRNA) conjugated to N-acetylgalactosamine (GalNAc) has become the most productive delivery platform in cardiovascular therapeutics. A triantennary GalNAc ligand binds the asialoglycoprotein receptor, which is expressed almost exclusively on hepatocytes and recycles every 15 minutes, so a subcutaneous injection delivers the duplex to the liver with unusual precision. Chemical stabilisation resists nuclease degradation, and a slowly released endosomal depot uncouples a plasma half-life of hours from a pharmacodynamic effect lasting months. Because the RNA-induced silencing complex acts catalytically, one loaded complex cleaves many transcripts, which is why dosing every three to six months is achievable. This review describes the pharmaceutical basis of the platform and the clinical evidence for agents directed at PCSK9, lipoprotein(a), APOC3, ANGPTL3, angiotensinogen and transthyretin. Surrogate endpoint data are substantial, but only vutrisiran has so far demonstrated reduced cardiovascular mortality and hospitalisation, and the failure of a lipoprotein(a)-lowering antisense agent to reduce events is a caution against assuming that biochemical efficacy will translate. The platform is also confined to hepatocyte-expressed targets, its effects cannot be rapidly withdrawn, and cost remains the decisive barrier to use in India.

KEYWORDS

Sirna, Galnac Conjugate, Inclisiran, Lipoprotein(a)

INTRODUCTION

Cardiovascular pharmacotherapy has depended on small molecules taken daily and, more recently, on monoclonal antibodies given every two to four weeks. Adherence erodes with both. RNA interference offers a different proposition: rather than blocking a protein, it prevents the protein from being made, and it does so for months after a single subcutaneous injection.

The obstacle was never the chemistry of silencing but delivery. Conjugation to N-acetylgalactosamine (GalNAc) solved it for the liver, which is where most cardiovascular drug targets are expressed. Eight agents built on this platform now hold cardiovascular indications or are in phase 3 trials. This review describes how the platform works, what the clinical evidence shows, and what limits its use.

PHARMACEUTICAL BASIS OF THE PLATFORM

Mechanism. A synthetic double-stranded siRNA is taken up by the RNA-induced silencing complex (RISC). The passenger strand is discarded and the guide strand directs Argonaute-2 to cleave the complementary messenger RNA. Cleavage is catalytic, so a single loaded complex destroys many transcripts; this, rather than any property of the molecule's own disposition, is what makes infrequent dosing possible (Springer & Dowdy, 2018).

Hepatocyte targeting. A triantennary GalNAc ligand binds the asialoglycoprotein receptor, present at roughly 500,000 copies per hepatocyte and recycling every 15 minutes. Multivalent GalNAc conjugates therefore localise to hepatocytes and produce robust silencing after subcutaneous injection, at doses far below those needed for unconjugated siRNA (Nair et al., 2014).

Intracellular trafficking. Once bound, the receptor-conjugate complex is internalised through clathrin-coated pits. The receptor returns to the sinusoidal membrane within minutes, while the conjugate passes into the endosomal compartment, where acidification separates ligand from receptor. Only a small fraction escapes into the cytosol to engage RISC; the remainder is retained in acidic vesicles and released gradually. It is this intracellular depot, rather than any plasma reservoir, that sustains silencing between doses. The sequence — subcutaneous injection, receptor-mediated uptake, endosomal retention, slow cytosolic release and catalytic cleavage — explains why an agent cleared from plasma within hours continues to suppress its target for months.

Chemical stabilisation. Alternating 2'-O-methyl and 2'-fluoro substitutions with terminal phosphorothioate linkages resist nuclease attack and raise potency several-fold (Nair et al., 2017; Egli & Manoharan, 2023). The class safety profile is dominated by injection-site reactions, without the hepatotoxicity signal seen with earlier

unconjugated oligonucleotides (Janas et al., 2018). Injection-site reactions remain the commonest adverse event across the clinical programmes and have rarely caused discontinuation.

COMPARISON WITH OTHER MODALITIES

The contrast with monoclonal antibodies is instructive. An antibody binds circulating PCSK9 stoichiometrically and must be replaced as it is cleared, so dosing is every two to four weeks. An siRNA removes the template instead, and because silencing is catalytic the interval extends to six months. GalNAc-conjugated antisense oligonucleotides occupy an intermediate position: they also recruit an enzymatic mechanism, RNase H, but are given monthly. Olezarsen and plozasiran address the same APOC3 transcript on monthly and three-monthly schedules respectively, which illustrates the dosing advantage conferred by RISC-mediated catalysis.

CLINICAL EVIDENCE BY TARGET

PCSK9. Inclisiran, 284 mg subcutaneously on day 1, at three months and then six-monthly, lowered low-density lipoprotein cholesterol by a placebo-corrected 50.6 per cent at day 90 in a patient-level analysis of the ORION-9, -10 and -11 trials (Ray et al., 2023). Outcome data are awaited: ORION-4 randomised 16,124 patients with established atherosclerotic disease (Bowman et al., 2026). Until it reports, inclisiran remains a lipid-lowering option rather than a proven event-reducing therapy. In VICTORION-Difference, 84.9 per cent of patients on an inclisiran-based strategy reached their guideline cholesterol goal at day 90 against 31 per cent on individually optimised usual care, with fewer muscle-related adverse events.

Lipoprotein(a). Lp(a) is genetically determined, raised in about one person in five, and unaffected by statins; no targeted therapy is approved. Olpasiran at 75 mg or more every 12 weeks reduced Lp(a) by more than 95 per cent at week 36 (O'Donoghue et al., 2022). A single 400 mg dose of lepodisiran gave a placebo-adjusted, time-averaged reduction of 93.9 per cent between days 60 and 180 (Nissen et al., 2025), and zerlasiran achieved 81 to 86 per cent reduction over 36 weeks of treatment (Nissen et al., 2024). These results must now be read against the phase 3 failure of pelacarsen, a GalNAc-conjugated antisense oligonucleotide, which lowered Lp(a) substantially in 8,323 patients without reducing major adverse cardiovascular events (Novartis, 2026). Whether deeper and more durable silencing changes that answer is the question the ongoing siRNA outcome trials exist to settle.

APOC3 and ANGPTL3. Plozasiran, given three-monthly, was approved by the United States Food and Drug Administration in November 2025 for familial chylomicronaemia syndrome, having reduced triglycerides by a median 59 per cent relative to placebo and acute pancreatitis from 20 to 4 per cent (US FDA, 2025). Zodasiran

reduced triglycerides by 51 to 63 per cent and remnant cholesterol by 73 to 82 per cent at week 24 (Rosenson et al., 2024). In phase 3 trials in broader severe hypertriglyceridaemia, median triglyceride reductions at month 12 reached 79 to 81 per cent against about 27 per cent on placebo, with a significantly lower risk of a first episode of acute pancreatitis.

Angiotensinogen and transthyretin. Single doses of zilebesiran, 150 to 600 mg, lowered 24-hour ambulatory systolic pressure by 14.1 to 16.7 mmHg against placebo at three months, with angiotensinogen suppressed by 88 to 98 per cent (Bakris et al., 2024); in patients already taking two to four antihypertensive agents, a single 300 mg dose gave a placebo-adjusted office systolic reduction of 5.0 mmHg. Vutrisiran, 25 mg every three months, is the one agent with demonstrated outcome benefit: in HELIOS-B it reduced all-cause mortality and recurrent cardiovascular events in transthyretin amyloid cardiomyopathy (Fontana et al., 2025).

TABLE – 1
GalNAc-siRNA AGENTS IN CARDIOVASCULAR MEDICINE

Agent	Target	Dosing	Key efficacy	Status (Oct 2026)
Inclisiran	PCSK9	6-monthly	LDL-C –50.6%	Approved; outcomes awaited
Olpasiran	LPA	12-weekly	Lp(a) >95%	Phase 3
Lepodisiran	LPA	6-monthly	Lp(a) –93.9%	Phase 3
Zerlasiran	LPA	16–24-weekly	Lp(a) –81 to –86%	Entering phase 3
Plozasiran	APOC3	3-monthly	Triglycerides –59%	Approved for FCS
Zodasiran	ANGPT L3	Day 1, week 12	Triglycerides –51 to –63%	Phase 2b complete
Zilebesiran	AGT	3–6-monthly	Systolic pressure –14–17 mmHg	Phase 3
Vutrisiran	TTR	3-monthly	Lower mortality, fewer events	Approved for ATTR-CM

Source: compiled by the authors.

LIMITATIONS AND THE INDIAN PERSPECTIVE

Three limitations deserve emphasis. The platform is confined to targets expressed in hepatocytes, because the asialoglycoprotein receptor is what makes delivery work; extrahepatic silencing remains unsolved. Durability cuts both ways, since an adverse effect cannot be withdrawn by stopping the drug. And most of the evidence rests on surrogate endpoints. Head-to-head comparisons against established oral therapy are absent, follow-up beyond three years is limited, and no trial has yet reported in an Indian population, in whom lipoprotein(a) distribution and the age of onset of coronary disease differ from those studied.

Cost is the decisive issue in India. Inclisiran has been reported at a price well beyond routine use in the public sector, and commentary at its Indian launch questioned its value against established oral therapy (Indo-Asian News Service, 2024). Unless price negotiation or domestic manufacture intervenes, these agents will remain confined to selected patients with familial hypercholesterolaemia, statin intolerance or amyloid cardiomyopathy.

CONCLUSION

GalNAc-siRNA conjugates represent a genuine pharmaceutical advance: precise hepatocyte delivery, catalytic silencing and dosing intervals measured in months. The biochemical efficacy is not in doubt. What remains unsettled is whether it converts into fewer cardiovascular events for most of these targets, and whether the cost will ever permit their use at scale in India.

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