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REVIEW

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RNA therapeutics in cardiovascular disease: Emerging roles of siRNA and mRNA technologies beyond COVID-19 vaccines

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ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, prompting the search for novel and targeted therapies. RNA-based therapeutics, particularly small interfering RNA (siRNA) and messenger RNA (mRNA) technologies, have emerged as promising tools in the post-COVID era, offering precise gene-level modulation. siRNA molecules are being explored for silencing atherogenic genes like PCSK9 and ANGPTL3, while mRNA platforms are being investigated for regenerative protein delivery, such as VEGF, to promote angiogenesis in ischemic tissues. This review highlights recent advances in RNA therapeutics for cardiovascular disorders, focusing on molecular targets, delivery challenges, and current clinical progress. It also discusses the role of lipid nanoparticles (LNPs) and other biotech-derived carriers in enhancing RNA stability and specificity. As RNA therapies move beyond infectious diseases, their potential in cardiovascular medicine is gaining rapid attention, paving the way for precision cardiology. Future integration with genomics and personalized medicine is expected to refine therapeutic outcomes further. With continued innovation, RNA platforms may soon complement or even replace traditional cardiovascular interventions.

KEYWORDS

RNA therapeutics; Cardiovascular disease; siRNA; mRNA therapy; Lipid nanoparticles (LNPs)

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, accounting for an estimated 18 million deaths annually, according to the World Health Organization (WHO) [1]. Despite significant advancements in pharmacological interventions and surgical techniques, existing therapies often target downstream effects rather than addressing the root molecular causes of disease. In this context, RNA-based therapeutics have emerged as a transformative approach, offering high specificity, programmability, and the ability to modulate gene expression at the source [2].

The global success of mRNA vaccines during the COVID-19 pandemic has catalyzed interest in RNA technologies across other therapeutic domains, including cardiology [3]. RNA therapeutics—comprising small interfering RNA (siRNA), messenger RNA (mRNA), antisense oligonucleotides (ASOs), and microRNA mimics—have demonstrated potential in modulating cardiovascular risk factors, regenerating damaged heart tissue, and preventing disease progression [4]. Among these, siRNA and mRNA are gaining rapid traction due to their clinical translatability and recent approval for non-infectious diseases [2,3].

siRNA-based approaches offer gene silencing capabilities that can downregulate harmful proteins such as proprotein convertase subtilisin/kexin type 9 (PCSK9), a key player in hypercholesterolemia [5]. Meanwhile, mRNA therapeutics hold promise in expressing beneficial proteins like vascular endothelial growth factor (VEGF), critical for promoting angiogenesis in ischemic heart tissue. However, challenges related to stability, delivery, immunogenicity, and tissue specificity remain significant barriers to widespread application [6].

This review aims to explore the current landscape of RNA therapeutics in cardiovascular disease, with a focus on siRNA and mRNA technologies. We will discuss therapeutic targets, delivery platforms, clinical progress, and biotech innovations shaping the future of RNA-based cardiovascular medicine.

siRNA Therapeutics in Cardiovascular Disease

Small interfering RNA (siRNA) has emerged as a powerful tool for silencing disease-associated genes at the post-transcriptional level. In cardiovascular medicine, this approach offers the potential to precisely downregulate key molecular targets involved in the pathogenesis of atherosclerosis, hyperlipidemia, hypertension, and cardiomyopathies [7]. The mechanism of siRNA involves the incorporation of double-stranded RNA into the RNA-induced silencing complex (RISC), which guides the complex to complementary mRNA strands, leading to their degradation and subsequent suppression of protein translation [8].

Key therapeutic targets

One of the most prominent targets in cardiovascular siRNA research is PCSK9 (proprotein convertase subtilisin/kexin type 9), an enzyme that plays a major role in LDL receptor degradation. Inhibition of PCSK9 leads to increased recycling of LDL receptors and enhanced clearance of low-density lipoprotein cholesterol (LDL-C) from the bloodstream [9]. This pathway is particularly relevant for patients with familial hypercholesterolemia or statin intolerance.

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Inclisiran, the first FDA- and EMA-approved siRNA-based therapy for cardiovascular indications, specifically targets PCSK9 mRNA in hepatocytes. Administered twice a year, Inclisiran has shown sustained LDL-C reduction with a favorable safety profile, marking a significant milestone in the clinical use of RNA interference for lipid management [10].
Other promising siRNA targets include:

- **ANGPTL3 (angiopoietin-like 3):** Involved in triglyceride and cholesterol metabolism, and its inhibition has been shown to reduce both LDL and triglyceride levels [11].
- **LPA (lipoprotein(a)):** Elevated levels are associated with a higher risk of atherosclerosis and myocardial infarction. siRNA-based approaches are being investigated to lower Lp(a) levels [12].

Advantages of siRNA over traditional therapies

siRNA therapeutics offer several distinct advantages [13]:

- **High specificity:** Designed to target unique mRNA sequences, minimizing off-target effects.
- **Long-lasting effects:** Some siRNA therapies maintain gene silencing for weeks to months after a single dose.
- **Lower dosing frequency:** Reduced treatment burden compared to daily oral medications.

Mechanism and applications of siRNA therapeutics

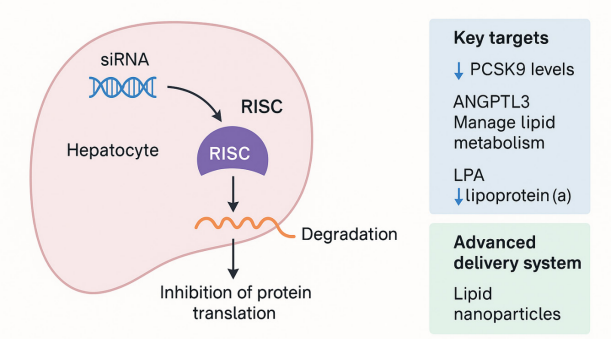

Figure 1. Mechanism and Applications of siRNA Therapeutics in Cardiovascular Disease.

This infographic (Figure 1) depicts the mechanism of siRNA-mediated gene silencing and its emerging therapeutic applications in cardiovascular disease. Delivered into target cells—primarily hepatocytes—siRNA molecules are incorporated into the RNA-induced silencing complex (RISC), which guides the degradation of specific mRNA transcripts, thereby inhibiting the production of disease-related proteins. Major targets include PCSK9 (to lower LDL-C), ANGPTL3 (to regulate lipid metabolism), and LPA (to reduce lipoprotein(a) levels). Advanced delivery technologies such as lipid nanoparticles and GalNAc conjugates are crucial in enhancing stability and tissue specificity [14].

Challenges in clinical translation

Despite these benefits, the use of siRNA in cardiovascular disease still faces several challenges. Targeted delivery remains a critical hurdle, as siRNAs must reach specific tissues, particularly the liver and vascular endothelium, without being degraded in the bloodstream. **Lipid nanoparticles (LNPs)** and **GalNAc conjugates** are among the most advanced delivery strategies currently in clinical use. Additionally, issues such as immune activation, off-target silencing, and renal clearance need to be carefully managed through chemical modifications and optimized formulations [15].

Current clinical landscape

The success of Inclisiran has inspired the development of next-generation siRNA candidates targeting other cardiovascular genes. Several agents are in various phases of clinical trials, showing promise for future approval [16]. Moreover, ongoing research aims to expand siRNA applications beyond lipid regulation into heart failure, arrhythmias, and vascular inflammation.

mRNA Therapeutics for Cardiac Repair

Messenger RNA (mRNA) therapeutics represent a groundbreaking frontier in cardiovascular medicine, expanding beyond their success in infectious disease vaccines to offer regenerative and cardioprotective therapies [3]. Unlike DNA-based interventions, mRNA therapies do not integrate into the host genome and are translated directly in the cytoplasm, making them safer and more adaptable for transient protein expression. These qualities make mRNA especially attractive for applications such as cardiac repair following myocardial infarction (MI), ischemia, or heart failure [16].

Rationale for mRNA in cardiac repair

Cardiac tissue has limited intrinsic regenerative capacity, and myocardial injury often results in irreversible loss of function. mRNA-based therapeutics aim to counteract this by transiently expressing proteins that promote [17]:

- **Angiogenesis** – Enhancing blood vessel formation in ischemic regions.
- **Cardiomyocyte survival** – Preventing cell death under oxidative stress.
- **Tissue remodeling** – Supporting structural and functional cardiac repair.

Key mRNA targets and strategies

A prominent target in cardiovascular mRNA therapy is **vascular endothelial growth factor A (VEGF-A)**, a protein central to angiogenesis. Modified VEGF-A mRNA delivered into ischemic myocardium has been shown to stimulate neovascularization and improve perfusion [18]. Phase I clinical trials have demonstrated the safety and feasibility of VEGF-A mRNA injections during coronary artery bypass grafting (CABG), marking an important translational milestone.
Other promising targets include [18]:

- **Fibroblast growth factor 2 (FGF2)** – Enhances endothelial cell proliferation.
- **Stromal cell-derived factor 1 (SDF-1)** – Recruits stem cells to injury sites.
- **Hepatocyte growth factor (HGF)** – Promotes anti-apoptotic and regenerative signaling.

Delivery platforms and stability considerations

Effective delivery and stability remain core challenges in mRNA

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therapeutics. Unmodified mRNA is prone to degradation by nucleases and can trigger immune responses. To address this, developers utilize [19]:

- **Chemically modified nucleotides** (e.g., pseudouridine, 5-methylcytidine) to improve stability and translation.
- **Lipid nanoparticles** (LNPs) for systemic or localized delivery.
- **Hydrogel-based scaffolds** for sustained release in cardiac tissue post-MI.

These innovations enhance tissue targeting, minimize toxicity, and ensure efficient protein expression where needed.

Current progress and future directions

Preclinical studies continue to show that mRNA therapies can improve cardiac function, reduce fibrosis, and support neovascularization in animal models of MI. Clinical trials are in early phases, focusing on safety, bioactivity, and optimization of dosing regimens. Ongoing research also explores combination approaches involving mRNA with biomaterials or stem cells to synergistically improve therapeutic efficacy [20].

As manufacturing techniques evolve and regulatory pathways mature, mRNA-based cardiac repair strategies could become viable adjuncts or alternatives to conventional surgical and pharmacological treatments.

Mechanism and applications of mRNA therapeutics

mRNA therapeutics function by delivering synthetic transcripts into target cells—typically cardiomyocytes or endothelial cells—where they are translated into therapeutic proteins [21]. These proteins initiate biological processes like angiogenesis, cell survival, and extracellular matrix remodeling that are critical for cardiac repair.

Therapeutic applications include:

- **Post-MI recovery** – Enhancing perfusion and limiting scar formation.
- **Chronic ischemia** – Supporting tissue viability in low-oxygen environments.
- **Heart failure prevention** – Protecting cardiac tissue during early stress phases.

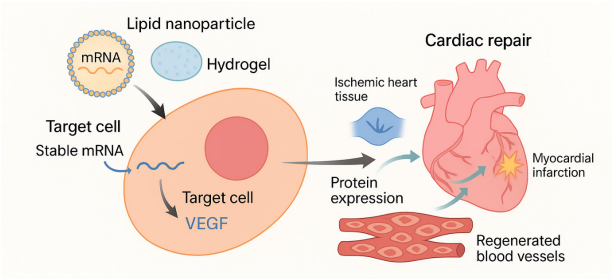

Figure 2. Mechanism and Application of mRNA Therapeutics for Cardiac Repair.

This illustration shows the role of mRNA therapy in inducing the expression of therapeutic proteins, such as VEGF-A, to promote angiogenesis, tissue regeneration, and functional recovery after myocardial injury. Synthetic mRNA is delivered into cardiomyocytes or surrounding endothelial cells using lipid nanoparticles or hydrogel-based carriers. Once inside the cytoplasm, the mRNA is translated into target proteins, triggering processes such as neovascularization and anti-apoptotic signaling [22]. This transient protein expression aids in restoring perfusion and structural integrity of the injured myocardium (Figure 2).

Delivery Platforms and Challenges

Efficient delivery is the cornerstone of successful RNA-based therapeutics in cardiovascular medicine. siRNA and mRNA molecules are inherently unstable, susceptible to enzymatic degradation, and may trigger immune responses. Moreover, targeting the cardiovascular system, especially the heart, with high specificity remains a major challenge due to anatomical complexity and rapid circulation dynamics [22].

Lipid nanoparticles (LNPs)

LNPs are currently the most widely used platform for both siRNA and mRNA delivery. Their structure enables encapsulation and protection of RNA molecules, facilitating cellular uptake via endocytosis. In the context of cardiovascular therapy, researchers are modifying LNP composition and surface characteristics to target endothelial cells or cardiomyocytes more effectively [23].

Advantages include:

- High RNA payload capacity
- Scalability for clinical use
- Enhanced intracellular delivery and endosomal escape

Limitations include potential immunogenicity, systemic distribution, and reduced efficacy in tissues outside the liver without targeted modifications.

GalNAc conjugates

GalNAc (**N-acetylgalactosamine**) conjugates are highly effective for delivering siRNA to the liver by binding to the asialoglycoprotein receptor (ASGPR) on hepatocytes. This platform has been successfully employed in FDA-approved therapies like inclisiran for lowering LDL-C by targeting PCSK9 [24].

While its liver specificity makes it ideal for treating lipid-related cardiovascular risks, its limited utility for heart-specific targeting remains a challenge.

Hydrogel- and polymer-based systems

Hydrogels and biodegradable polymers offer a unique solution for localized delivery of mRNA therapies, particularly in post-myocardial infarction (MI) settings. These materials allow for sustained, site-specific release of therapeutic RNA directly into damaged myocardial tissue [25].

They can be engineered for injectability, pH sensitivity, and biocompatibility, although reproducibility and degradation control are still areas of active research.

Comparative overview of RNA delivery systems

To summarize the advantages and limitations of each major delivery platform used in cardiovascular RNA therapeutics, the following table provides a comparative overview (Table 1).

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Table 1. Comparison of RNA delivery platforms in cardiovascular therapeutics [26].

Delivery Platform	Type of RNA	Target Tissue	Advantages	Limitations
Lipid Nanoparticles (LNPs)	siRNA, mRNA	Liver, Heart (in development)	High efficiency, scalable, endosomal escape	Immunogenicity, off-target accumulation
GalNAc Conjugates	siRNA	Liver (hepatocytes)	Subcutaneous delivery, highly specific, low immunogenicity	Limited to liver-targeted therapies
Hydrogel-based Systems	mRNA	Myocardium (post-MI sites)	Sustained release, local delivery, biocompatible	Reproducibility, degradation variability
Polymer-based Nanocarriers	siRNA, mRNA	Heart, vasculature (preclinical)	Tunable properties, possible cardiac targeting	Complex formulation, in vivo biocompatibility needs assessment

Remaining challenges

Despite promising progress, several key barriers must be addressed to advance RNA therapeutics in cardiovascular care:

- **Tissue specificity:** Achieving precise delivery to cardiac or vascular tissues remains difficult.
- **Safety and immune tolerance:** Avoiding innate immune responses while ensuring long-term safety.
- **Scalability and manufacturing consistency:** High-quality RNA synthesis and reproducible formulation processes are essential for clinical translation.
- **Regulatory and clinical validation:** Robust safety and efficacy data are needed to navigate complex approval processes.

Overcoming these hurdles will be essential to fully realize the potential of RNA-based platforms in treating cardiovascular disease.

Future Perspectives

The future of RNA-based therapeutics in cardiovascular disease looks exceptionally promising, driven by rapid advancements in RNA biology, nanotechnology, and precision medicine. While early success has been achieved in lipid regulation and gene silencing, especially with siRNA technologies, many opportunities remain to expand the scope and improve the specificity, safety, and clinical application of these novel therapies [8].

Targeting tissues beyond the liver

Current delivery systems, particularly GalNAc-siRNA conjugates, are highly effective for liver-targeted therapies but are less suitable for cardiac and vascular tissues. Moving forward, developing delivery platforms that can precisely target the heart, blood vessels, or inflammatory cells involved in cardiovascular disease is essential [26]. Promising strategies include ligand-decorated nanoparticles, cell-penetrating peptides, and exosome-based carriers that offer tissue-specific delivery and improved biocompatibility.

Advancements in mRNA therapy

The success of mRNA vaccines has accelerated interest in therapeutic mRNA for cardiac repair and regeneration. Future directions involve designing mRNA constructs that can express multiple regenerative proteins, improving mRNA stability and translation efficiency, and reducing immunogenicity. Researchers are also exploring responsive delivery systems that can release mRNA selectively in damaged myocardial tissue or under ischemic conditions, enhancing therapeutic precision [27].

Personalized RNA therapeutics

With progress in genetic profiling and biomarker discovery, the field is moving toward personalized RNA therapies tailored to an individual's genetic risk factors, disease phenotype, and response to treatment. This approach could significantly improve the effectiveness of RNA-based interventions in complex cardiovascular diseases, where one-size-fits-all therapies often fall short [28].

Clinical translation and regulatory progress

The path from laboratory innovation to clinical application remains a key challenge. Ensuring long-term safety, minimizing immune responses, and standardizing manufacturing processes are critical steps for clinical translation. Regulatory agencies are now adapting to these new classes of drugs, but further clarity on guidelines for chronic and combination RNA therapies will be vital to accelerate approval and adoption.

Conclusions

RNA-based therapeutics represent a transformative frontier in the treatment of cardiovascular disease. siRNA technologies have already begun to reshape lipid management by enabling targeted gene silencing, while mRNA therapeutics offer new possibilities for myocardial repair and regeneration through transient protein expression. Together, these platforms provide a novel framework for precise, programmable interventions in conditions where conventional therapies often fall short.

Despite substantial progress, several challenges remain, especially in achieving tissue-specific delivery, minimizing immune responses, and ensuring long-term safety. Innovations in delivery technologies, such as lipid nanoparticles, GalNAc conjugates, and hydrogel systems, are helping overcome many of these limitations. Moreover, as our understanding of cardiovascular genomics deepens, RNA therapeutics are expected to play a central role in the evolution of personalized

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and regenerative cardiology.

With continued interdisciplinary collaboration and investment in translational research, RNA therapies are likely to become a core component of the future cardiovascular treatment landscape, offering safer, more efficient, and more adaptable solutions to some of the most pressing challenges in heart health.

Disclosure statement

The authors declare that they have no competing interests.

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