

RNA Therapeutics in Cardiovascular Disease: Hype or Hope?

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Abstract

RNA-based therapeutics have transformed clinical practice in oncology, rare diseases, and infectious diseases, yet their application in Cardio Vascular Disease (CVD) remains limited. This mini-review explores the therapeutic potential of various RNA modalities-including siRNA, Anti-Sense Oligonucleotides (ASOs), messenger RNA (mRNA), and circular RNA (circRNA)-in the context of CVD. It highlights recent advances, such as the approval of Inclisiran for lipid lowering and clinical trials of VEGF-A mRNA for cardiac regeneration. The review also examines major translational challenges, particularly in achieving tissue-specific delivery to the heart. Finally, it outlines emerging strategies such as RNA-based polypharmacology and cardiac-targeted delivery platforms, emphasizing that while RNA therapeutics are not a universal solution, they offer credible potential for precision cardiovascular medicine.

Keywords: RNA-Based Therapeutics; Cardio Vascular Diseases/Therapy; Small Interfering RNA (siRNA); Messenger RNA (mRNA)/Pharmacology; Drug Delivery Systems/Methods; Non-Coding RNA/Therapeutic Use

Introduction

The field of RNA therapeutics has experienced remarkable growth in the last decade, with breakthroughs ranging from small interfering RNAs (siRNAs) to messenger RNA (mRNA) vaccines. These molecules offer unprecedented precision in modulating gene expression, enabling therapeutic strategies that were once considered unattainable. In oncology and rare genetic diseases, RNA-based drugs have moved swiftly from bench to bedside, with approved products now altering clinical paradigms. However, in Cardio Vascular Disease (CVD)-the leading global cause of death-the momentum has been slower. Despite the biological complexity and high unmet medical need, RNA therapies have yet to penetrate the mainstream of cardiology. Is this delay a consequence of delivery challenges, disease heterogeneity, or a misalignment between innovation and clinical applicability? This article examines whether RNA therapeutics are a realistic hope for cardiovascular medicine or simply the latest hype, by reviewing current modalities, translational barriers, and future prospects.

The Molecular Promise: RNA Modalities in CVD

RNA-based therapeutics encompass a diverse set of platforms including Anti-Sense Oligonucleotides (ASOs), siRNAs, microRNA mimics (miR-Mimic), and long non-coding RNAs (lncRNAs), small activating RNAs (saRNAs), and more recently, messenger RNAs (mRNAs) and circular RNAs (circRNAs) [1-3]. Each offers distinct mechanisms to regulate gene expression, from silencing pathogenic transcripts to encoding therapeutic proteins. Among these, siRNAs and ASOs have shown the most clinical traction. The landmark approval of Inclisiran, a GalNAc-conjugated siRNA targeting hepatic PCSK9, marked a turning point for RNA therapeutics in lipid management [4]. This agent lowers LDL-C with biannual dosing, offering a viable

alternative for patient's intolerant to statins. Though Inclisiran acts on the liver, its ultimate benefit lies in cardiovascular risk reduction, indirectly validating RNA's role in CVD prevention [5,6]. Meanwhile, mRNA technologies-brought into the spotlight by the COVID-19 vaccines-are being repurposed for cardiac regeneration. Clinical trials using VEGF-A mRNA (e.g., AZD8601) aim to promote angiogenesis in ischemic myocardium. Preclinical studies are also investigating mRNA-based expression of protective proteins, such as eNOS and SOD2, in models of heart failure and ischemia-reperfusion injury. Beyond their preventive applications, mRNA technologies are being explored for their therapeutic potential in treating established diseases. Our recent preclinical studies have yielded promising data demonstrating the beneficial effects of both linear mRNAs and translatable circular mRNAs in models of diabetic skin wound healing and experimental heart failure (patents under review). Beyond these, emerging interest surrounds circRNAs and lncRNAs as both biomarkers and therapeutic targets in myocardial hypertrophy, arrhythmogenesis, and fibrosis [7]. Though their translation remains nascent, these non-coding RNAs offer a novel layer of regulation distinct from traditional coding paradigms. Collectively, these RNA platforms promise unprecedented precision in cardiovascular intervention. Yet, their clinical impact will ultimately hinge on safe, efficient, and tissue-specific delivery-a major barrier we explore next.

The Delivery Dilemma

Despite the therapeutic potential of RNA-based modalities, their success in cardiovascular disease hinges on a major challenge: Delivery [8]. Unlike small molecules, RNA drugs are inherently unstable, immunogenic, and require protection and precise targeting to reach their intracellular site of action. In practice, this has restricted the clinical success of RNA therapies to tissues with permissive uptake-chieflly the liver. The liver's fenestrated endothelium and natural role in metabolizing circulating molecules have made it an ideal target for RNA delivery via GalNAC-conjugation or lipid nanoparticles. In contrast, the heart poses formidable barriers. Cardiomyocytes are shielded by a continuous endothelium with limited permeability, and the myocardium itself is characterized by high perfusion, mechanical motion, and a dense extracellular matrix-all of which impair nanoparticle accumulation and uptake.

Current delivery strategies under investigation for cardiac targeting include:

Cardiac-homing peptides (e.g., CTP, CAR): These peptides can be conjugated to nanoparticles or oligonucleotides to enhance myocardial specificity. Some have shown promise in preclinical models, but few have advanced to human trials [9].

Lipid and polymeric nanoparticles: Optimized formulations seek to improve cardiac tropism, often with modifications to surface charge, size, or ligand display. However, most still accumulate in the liver or spleen [10,11].

Extracellular vesicles and exosomes: These natural carriers exhibit intrinsic tissue tropism and low immunogenicity, but their

manufacturing, standardization, and scalability remain unresolved [12].

Aptamer and antibody-conjugated systems: These offer higher specificity but add complexity in design and cost [13,14].

To date, no RNA therapeutic with primary myocardial delivery has received regulatory approval. Until this barrier is overcome, the promise of RNA therapies in CVD will remain largely theoretical.

Clinical Translation: Where Do We Stand?

While the molecular platforms and delivery technologies continue to advance, the clinical translation of RNA therapeutics in cardiovascular disease remains limited. As of now, the only RNA-based drug with demonstrated cardiovascular benefit is Inclisiran-and even this acts indirectly by targeting hepatic PCSK9 to lower LDL-C, rather than engaging the myocardium or vasculature directly. Early attempts to apply mRNA therapy in cardiology have focused primarily on ischemic heart disease. Notably, AZD8601, an mRNA encoding vascular endothelial growth factor-A (VEGF-A), has been tested in patients with coronary artery disease undergoing coronary bypass surgery [15,16]. The rationale: Localized delivery of VEGF-A mRNA to promote angiogenesis in ischemic myocardium. Initial phase 1/2a data (EPICURE trial) demonstrated safety and some signs of efficacy, but robust clinical benefit remains unproven.

Beyond ischemia, preclinical investigations are exploring mRNA and oligonucleotide therapies in a variety of cardiac conditions, including:

- A. Dilated and hypertrophic cardiomyopathies (e.g., targeting titin truncating mutations or abnormal calcium handling),
- B. Myocarditis and post-infarction remodeling (e.g., via anti-inflammatory siRNAs),
- C. Heart failure with preserved ejection fraction (HFpEF), where non-coding RNAs modulate fibrosis, endothelial dysfunction, and inflammation.

Despite this activity, no RNA therapy to date has achieved myocardial or vascular targeting in humans. Most programs remain in early-phase or preclinical development, hindered by delivery inefficiencies, limited disease-specific biomarkers, and the complex pathophysiology of CVD, which is rarely monogenic.

In essence, while the therapeutic pipeline is expanding, meaningful clinical translation in cardiology remains in its infancy.

Hype or Hope?

The excitement surrounding RNA therapeutics in cardiovascular disease is both justified and cautionary. On one hand, the conceptual appeal is undeniable: RNA drugs offer target specificity, rapid design cycles, and the flexibility to modulate disease processes at the transcriptional or translational level. They are ideally suited for precision medicine-provided the right target, delivery method, and patient population can be identified. Yet, the hype often outpaces reality. Most RNA platforms remain limited to hepatic or oncologic applications, where delivery is more tractable and clinical

endpoints are more direct. In contrast, cardiovascular diseases are inherently multifactorial, involving complex interactions among neurohormonal, inflammatory, metabolic, and structural pathways. Targeting a single RNA species may not suffice for meaningful clinical impact, especially in syndromic conditions like heart failure or atherosclerosis. Moreover, delivery remains the Achilles' heel. Without robust, reproducible, and tissue-specific delivery systems, even the most promising RNA candidates may fail in translation. The heart, unlike the liver, is not naturally accessible to standard RNA delivery platforms. Nonetheless, there is reason for hope. Advances in cardiac-homing nanoparticles, AI-guided oligonucleotide design, and systems biology are beginning to bridge the gap between RNA technology and cardiovascular application. Novel approaches-such as modular RNA editing tools (e.g., Cas13), synthetic circRNAs with enhanced stability, and multi-RNA-target strategies-may overcome current limitations. In short, RNA therapeutics are not panacea, but neither are they overhyped. They represent a new frontier-one that demands rigorous translational science, targeted innovation, and tempered expectations.

Conclusion & Future Directions

RNA-based therapeutics have reshaped the pharmaceutical landscape, offering transformative treatments in areas once considered intractable. In cardiovascular disease, however, their journey has just begun. While Inclisiran provides a compelling proof-of-concept, the broader application of RNA modalities in cardiology remains constrained by delivery challenges, disease complexity, and a relative paucity of validated targets.

Looking ahead, progress will depend on overcoming three critical barriers:

1. Efficient and specific delivery to cardiac and vascular tissues
2. Better preclinical models that reflect human cardiovascular pathophysiology
3. Rational target selection based on systems biology and multi-omics data

Investment in cardiac-targeted delivery systems-such as antibodies homing peptides, smart nanoparticles, or engineered exosomes-will be essential. In parallel, evolving tools like RNA editing technologies and high-throughput screening platforms can accelerate the identification of viable therapeutic nodes. Additionally, the advent of RNA-based therapeutics marks a transformative advance in polypharmacology [3,17-20], offering innovative strategies to target the complex and interconnected mechanisms underlying cardiovascular diseases and other multifactorial conditions. Unlike traditional small molecules and protein-based therapies, RNA therapeutics can directly modulate gene expression, enabling precise intervention across multiple biological pathways simultaneously. This unique capability positions RNA-based approaches as powerful tools for addressing the multifaceted nature of aging and other complex disorders.

RNA-based polypharmacology-or multitarget RNA therapeutics [3]-involves the use of RNA molecules such as mRNA, siRNA, ASOs, saRNAs, and microRNA interference (miRNAi) technologies [2] to concurrently modulate multiple targets within a network of interconnected pathways.

Ultimately, the future of RNA therapeutics in cardiovascular disease is neither hype nor certainty-it is potential. With interdisciplinary innovation and a realistic understanding of translational hurdles, RNA-based strategies may yet redefine how we treat the world's leading cause of death.

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Author Contributions

Wang Z conceptualized the work and drafted the manuscript. Ju J refined the concept and performed editing, polishing, and proofreading of the manuscript.

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