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mRNA-Based Therapeutics and Vaccines in Atherosclerosis and Coronary Artery Disease: Emerging Immunomodulatory Strategies

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ABSTRACT

Atherosclerosis and coronary artery disease are two of the most severe cardiovascular conditions, which include lipid accumulation, endothelial dysfunction, chronic inflammation, and plaque instability. Although various medications are used to treat these conditions, such as statins, PCSK9 inhibitors, and anti-inflammatory agents, they don't always react positively in all patients. Some do not respond, and they cannot target all stages of disease development. Therefore, RNA-based therapy has become a novel treatment option for most cardiovascular diseases. The messenger RNA technology provides instructions for a cell to produce certain therapeutic proteins and can also be utilized in a sort of vaccine manner to modulate the immune system. In cardiovascular disease, specifically atherosclerosis and coronary artery disease, mRNA platforms are being investigated for potential applications in lipid metabolism and vascular immunomodulation. Immunomodulation includes regulation of T cells, including the balance between pro-inflammatory T cells and regulatory T cells (Tregs), as well as cytokine levels, like IL-1β, IL-6, and TNF-α. Accessible evidence suggests positive results in laboratory studies and some patient data regarding VEGF-A mRNA treatments. However, there are still several issues related to delivery, safety, activation, and sustainability of mRNA therapy. In the foreseeable future, research may involve investigation of vaccines, nanotechnology, combination therapy, and precision immunotherapy.

KEYWORDS: mRNA therapeutics, atherosclerosis, coronary artery disease, immunomodulation, lipid metabolism, inflammation, vaccines, nanotechnology

INTRODUCTION

Some of the most severe cardiovascular diseases include atherosclerosis (AS) and coronary artery disease (CAD), and they contribute substantially to global morbidity and mortality. Atherosclerosis is a chronic disease that involves the accumulation of lipids, inflammatory cells, extracellular matrix components, and cellular remnants within the artery wall, resulting in the development of atherosclerotic lesions. CAD occurs because of atherosclerotic lesions in the coronary arteries that end up cutting off the blood supply to the heart. Cardiovascular diseases are currently the number one cause of death, making it essential to develop preventive and therapeutic approaches (Bejar et al.). Atherosclerosis is very strongly linked to both lipid metabolism and inflammation. The rise in low-density lipoprotein (LDL) cholesterol helps lipids accumulate inside the walls of arteries. LDL can be oxidized, which leads to the activation of cells and attraction of monocytes and other inflammatory cells. After that, comes the uptake of oxidized LDL

by macrophages and the formation of foam cells, which cause plaque formation. Inflammation continues throughout the entire period of atherosclerosis development and may lead to the formation of vulnerable plaques and cardiovascular disease (Hetherington and Totary-Jain 2022). Therefore, lipid management alone cannot solve the entire atherosclerosis problem. The use of current drugs like statins is essential for lowering the LDL level and reducing the risk of heart disease; however, not all patients get satisfactory results in terms of lipid lowering, and there are also problems related to long-term therapy. The PCSK9 inhibitors can help with the further lowering of LDL, but their high price and need for repetitive use may cause problems regarding long-term therapy (Li et al. 2022). Another option that has been considered is anti-inflammatory drugs, considering that inflammation plays a key role in the development of atherosclerosis. In conjunction with RNA-based treatments, opportunities have emerged in relation to treating cardiovascular diseases using molecular targets. Some of the RNA-based medications include mRNA, siRNA, ASOs, and others that help regulate gene expression or produce therapeutic proteins (Bejar et al. 2022). One of the most promising RNA-based medications is mRNA due to the ability of this medication to provide temporary gene expression, which makes it possible to produce therapeutic proteins without altering the genetic structure of the host cell. In addition, advancements in the design and delivery of mRNA, such as lipid nanoparticles, have improved its application in cardiology (Pardi et al. 2018). The purpose of this review is to explore the possibility of using mRNA therapy in the context of atherosclerosis and coronary artery disease. The topics covered in the article include pathophysiology of AS and CAD, structure and function of mRNA, delivery methods, anti-atherosclerosis vaccination, mRNA therapy for cardiovascular diseases, immune mechanisms, current state of affairs in clinical studies, comparison to other RNA therapies, and further applications.

LITERATURE REVIEW METHODOLOGY

In this article, we review the potential use of mRNA therapeutics and vaccines in atherosclerosis and CAD with a focus on immunomodulation, lipid metabolism, vascular inflammation, and cardiovascular regeneration.

The literature was searched in PubMed, Scopus, and Google Scholar using relevant keywords, and publications from 2010 to 2026 were included. However, if relevant, studies before 2010 were also included.

They searched for combinations of “messenger RNA,” “mRNA therapeutics,” “mRNA vaccines” and “atherosclerosis” and combinations of “coronary artery disease,” “cardiovascular disease,” “immune tolerance,” “lipid nanoparticles,” “PCK9,” “ApoB” and “VEGF-A mRNA” and “cardiac regeneration.” Technologies other than mRNA-based were distinguished from mRNA using the following related searches: "small interfering RNA," "antisense oligonucleotides," and "anti-atherosclerotic vaccination.

Peer-reviewed original research articles, relevant clinical studies, and review articles covering the mechanisms of cardiovascular disease, therapeutic technologies based on RNA, immunomodulatory

strategies, and clinical translation were included. Comparative studies of non-mRNA technologies were included, but were not used as direct evidence of mRNA therapeutic effectiveness.

Publications were evaluated for their relevance to the review goals, molecular mechanism of the intervention, therapeutic platform used, and supporting evidence. Special focus was placed on discerning in vitro results, animal experiments, human clinical studies, and theoretical therapeutic suggestions.

This is a narrative review and there is no quantitative meta-analysis or pooled effect estimate. The results of the conclusions are designed to review and interpret the literature and not to prove clinical efficacy.

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

Atherosclerosis is an inflammatory condition that is considered to be the main contributor to Coronary Artery Disease. The process starts with endothelial dysfunction, where the inner lining of the blood vessels loses its functionality due to risk factors including hypertension, smoking, diabetes, obesity, and elevated cholesterol (Młynarska et al. 2025). Damaged endothelial cells become more permeable, which allows low-density lipoprotein cholesterol to enter the arterial wall. This leads to oxidative stress that decreases nitric oxide production, promoting inflammation and vascular damage (Penna and Pagliaro 2025). Inside the arterial wall, LDL particles undergo oxidation and become oxLDL (Akyol et al. 2025). OxLDL activates endothelial cells, which results in the production of adhesion molecules that attract monocytes to the site of the injury (Yang et al. 2025). Monocytes travel to the intimal layer, differentiate to macrophages, and take up oxLDL to form foam cells. The accumulation of foam cells creates fatty streaks, the earliest pathological changes in atherosclerosis. As inflammation progresses, smooth muscle cells enter the intima and produce collagen, contributing to plaque formation (Borén et al. 2025). Inflammation leads to the migration of smooth muscle cells and deposition of collagen to form atherosclerotic plaque.

Immune and Inflammatory Mechanisms

The processes of immunity and inflammation are key to the development and worsening of atherosclerosis and CAD. After endothelial dysfunction occurs, monocytes will enter the walls of the arteries and differentiate into macrophages. Macrophages take up oxidized low-density lipoprotein (oxLDL) molecules and become foam cells, which will accumulate in the intima layer and produce fatty streaks that will eventually lead to atherosclerosis (Akyol et al. 2025). Foam cells release more substances that cause inflammation and worsen the condition further. Another component of the inflammatory response in atherogenesis includes T lymphocytes, specifically T helper 1 cells (Th1) and regulatory T cells (Tregs). Th1 cells secrete pro-inflammatory cytokines to activate macrophages and cause damage to endothelial cells, whereas Tregs help in preventing the exaggerated reactions by the immune system. An imbalance favoring Th1 activity over Treg function results in inflammation and atherosclerosis (Zhili, Zhimin and Nenghua). The presence of inflammatory cytokines such as interleukin- 1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) causes further aggravation in the process of

endothelial dysfunction, vascular smooth muscle cell proliferation, and plaque formation (Penna and Pagliaro 2025). These cytokines amplify inflammatory signaling pathways and increase the risk of plaque rupture, thrombosis, and myocardial infarction associated with coronary artery disease.

Plaque Progression and Instability

As atherosclerosis progresses, the size of plaque within the arterial wall increases and the plaque becomes less stable, which causes an increased risk of coronary artery disease. The formation of atheromatous plaque continues with the buildup of oxLDL, inflammatory cells, and foam cells, leading to the development of larger atherosclerotic plaque (Akyol et al. 2025). Over time, macrophages and foam cells will undergo cell death and shed lipids, cholesterol crystals, and other cellular debris in the plaque, creating a necrotic core (Borén et al. 2025). The fibrous cap, which primarily consists of collagen and smooth muscle cells, normally protects the plaque from rupture. However, the inflammation triggers the release of MMPs by macrophages, enzymes that act on the degradation of collagen and extracellular matrix proteins, causing fibrous cap thinning (Penna and Pagliaro 2025). Reduced collagen production by smooth muscle cells makes the fibrous cap even more fragile, and this increases the risk of rupture. Thin-capped fibroatheromas are strongly associated with acute coronary events and are considered highly unstable. The rupture of the plaque leads to the exposure of thrombogenic material from the necrotic core in contact with blood, activating platelets and clotting of the blood. The resulting thrombus can partially or completely block coronary arteries, which leads to myocardial infarction or acute coronary syndrome (Zhili et al. 2025).

mRNA THERAPEUTICS: STRUCTURE, MECHANISMS, AND DELIVERY

Structure and Types of mRNA

Messenger RNA (mRNA) is a single-stranded nucleic acid strand carrying genetic code from DNA to the ribosomes for protein synthesis. In therapeutic mRNA, improvements are made in order to increase stability and protein expression. A conventional mRNA molecule consists of a 5’ cap, untranslated regions (UTRs), a coding region, and a poly (A) tail. These features allow protection against mRNA breakdown and ensure that translation into proteins takes place effectively (Pardi et al.). Standard mRNA works in such a way that the genetic code is delivered to the cells directly for further protein translation. Self-amplifying mRNA (saRNA) is an advanced form of mRNA technology that possesses genetic sequences for replicase proteins. Replicases enable replication of the RNA and the creation of many RNA copies inside cells, which leads to a dramatic increase in protein expression (Bloom et al. 2020). The saRNA is considered to be one of the most promising new technologies both for vaccinations and future medications. Modified nucleosides are commonly incorporated into synthetic mRNA to improve its performance. In particular, uridines can activate innate immune reactions and stimulate inflammatory processes, resulting in rapid destruction of RNA. Modified nucleosides like pseudouridine or N1-methylpseudouridine are used in place of uridines as they reduce immune activation and enhance the process of translation (Karikó et al. 2005).

Mechanism of Action

The mechanism of action of mRNA therapeutics includes the delivery of genes encoding particular proteins to cells. Following introduction to the body, mRNAs usually get enclosed in lipid nanoparticles (LNPs), thereby ensuring their protection and cellular entry (Pardi et al.). The LNPs penetrate the target cells by means of endocytosis, the process that involves engulfing of the LNPs by a cell membrane. Upon their entry into the cell, the mRNAs get released into the cytoplasm, becoming accessible to ribosomes, which synthesize proteins. In contrast to DNA therapies, mRNA enters neither the cell's nucleus nor interferes with the host's genome. Instead, ribosomes directly translate the mRNA sequence into a specific protein (Verbeke et al. 2019). As part of the translation process, transfer RNA shuttles the appropriate amino acids to the ribosomes to construct the specific protein using information from the mRNA. Once expressed, the protein could have either therapeutic benefits or activate the patient's immune system, based on the intended effect of mRNA therapy. After the translation process of the mRNA, it gets broken down by the cell's enzymes, limiting the effect to a certain period without changing the patient's genetic makeup (Pardi et al. 2018). This has made mRNA an exciting prospect in developing vaccines and novel treatment options for cardiovascular disease and other conditions.

Delivery Systems

Effective delivery is crucial in the successful administration of mRNA therapies since naked RNA is prone to degradation and is very susceptible to the actions of various enzymes found in the body. LNPs are the most commonly used vehicle for delivering mRNA therapies. LNPs have been shown to provide protection against degradation, help in the entry of mRNA into cells, and aid in the delivery of mRNA to the cytosol post-internalization (Hou et al. 2021). LNPs are made up of ionizable lipids, phospholipids, cholesterol, and PEG-lipids. Alternatively, there is another strategy based on the use of polymers for mRNA delivery. There are biodegradable polymers capable of binding and protecting mRNA as well as releasing it into the tissues in a targeted manner (Kowalski et al. 2019). While polymer carriers can be potentially more structurally flexible than LNPs, they often need additional modifications in order to achieve similar delivery efficiency (Kowalski et al. 2019). Targeted delivery is an area of research aimed at improving specificity and reducing off-target effects of the therapy. It relies on modification of nanoparticles with ligands, antibodies, or peptides recognizing certain cell surface receptors.

Advantages Over Traditional Therapies

There are various benefits associated with mRNA drugs compared to other therapies that use genes and proteins. The first benefit is the temporary expression. After being introduced into the cells, mRNA undergoes protein synthesis for some time, after which it is degraded by the cell's enzymes. Although temporary, it helps to achieve a desired effect without causing any problems related to long-term expression (Pardi et al. 2018). The second major benefit of using mRNA is that it does not involve genomic integration. This is because the mRNA molecule stays in the cytosol of the cell, making it impossible to enter the nucleus where it can be integrated. This makes the therapy safer compared to others that involve DNA molecules (Verbeke et al. 2019). Rapid design and scalability are additional

benefits associated with mRNA technology. After determining the genetic code of a target protein, it becomes easy and quick to manufacture an mRNA sequence. This ensures quick development of vaccines and treatment methods alongside streamlining the process of large-scale production when contrasted with standard protein medications (Pardi et al. 2018). This has been one of the reasons behind the increased popularity of mRNA in the treatment of infectious diseases, cardiovascular problems, and beyond.

ANTI-ATHEROSCLEROTIC VACCINATION AND IMMUNOMODULATION

Concept of Anti-Atherosclerotic Vaccination

Anti-Atherosclerotic vaccination is an identified approach to prevent plaque formation in arteries by controlling the immune system without the involvement of infectious agents. Traditional vaccinations work on inducing high immune responses to fight infectious agents. However, anti-atherosclerotic vaccinations seek to regulate the immune responses against the body's own antigens (Hansson and Nilsson 2020). With the understanding that atherosclerosis is a disease associated with inflammation and involves immune responses, vaccination becomes important. One of the major concepts in the development of vaccines surrounding the treatment of atherosclerosis is the interplay between immune tolerance and immune activation. Tolerance refers to the process of educating the immune system on how to identify antigens associated with diseases without causing damage via inflammation. On the other hand, pro-inflammatory immune activation may contribute to plaque progression and destabilization, whereas appropriately regulated immune responses may help limit vascular inflammation. The goal is to promote immune tolerance towards atherosclerosis antigens (Hansson and Nilsson 2020).

One key difference is that the majority of anti-atherosclerotic vaccine approaches that have been published have utilized peptide antigens, recombinant proteins, or other immunisation platforms that use non-mRNA. While these studies provide a biological basis for antigen-specific immune modulation, the results alone do not necessarily demonstrate the efficacy of mRNA vaccines. An anti-atherosclerotic vaccine, on the other hand, based on mRNA would supply a sequence of mRNA encoding the selected antigen under study, and the immune response elicited would rely on the antigen design, delivery vehicle, and inflammatory environment in which the antigen is presented. This is still experimental and needs to be directly tested (Hansson and Nilsson 2020; Moreno-Gonzalez et al. 2023; Raposo-Gutiérrez et al. 2023).

Target Antigens

There are several antigens that have been discovered and considered potentially important for the development of an anti-atherosclerotic vaccine. One of those most intensively researched is apolipoprotein B (ApoB), which is the major protein component of LDL. The peptides obtained from ApoB are capable of eliciting specific immune responses that prevent atherosclerotic lesion formation and lower inflammation (Raposo-Gutiérrez et al. 2023). Another equally significant target is proprotein convertase subtilisin/kexin type 9 (PCSK9), which is a protein that is associated with cholesterol metabolism. The role of PCSK9 is to increase the degradation of LDL receptors, causing an increase in

the concentration of LDL cholesterol in circulation. Antibody-based vaccines against PCSK9 increase LDL receptors and promote the elimination of LDL from the bloodstream (Moreno-Gonzalez et al. 2023). Oxidized LDL (oxLDL) epitopes are also good candidates for vaccination due to their direct involvement in endothelial dysfunction, foam cell formation, and vascular inflammation. Experimental immunization against oxLDL-related epitopes has been investigated as a potential means of modulating atherogenic immune response (Raposo-Gutiérrez et al. 2023).

Mechanisms of Immunomodulation

Experimental anti-atherosclerotic vaccination strategies aim to modify antigen-specific immune responses to reduce vascular inflammation. The mechanisms and outcomes depend on the vaccine platform and antigen employed. Tregs are essential for maintaining tolerance in the immune system, suppressing excessive immune reactions, and producing anti-inflammatory cytokines to reduce inflammation in blood vessels (Lecis et al.). Anti-atherosclerotic vaccines also suppress inflammation by inhibiting the functioning of inflammatory T cells and macrophages. The result is decreased levels of inflammatory cytokines including IL-1β, IL-6, and TNF-α, which are known to be related to the growth and destabilization of atherosclerotic plaques (Engelen et al. 2022). With lowered levels of cytokines, there is less recruitment of immune cells as well as fewer foam cells created. Moreover, vaccines that can target specific antigens like PCSK9 and oxLDL through antibodies could help in lowering cholesterol and neutralizing any toxic lipids in the body, thereby offering immunological and metabolic advantages. These findings support further investigation of antigen-specific immunomodulation, but clinical efficacy and safety in humans have not been established for mRNA-based anti-atherosclerotic vaccines. (Moreno-Gonzalez et al. 2023).

THERAPEUTIC APPLICATIONS OF mRNA IN CARDIOVASCULAR DISEASES

Protein Replacement Strategies

One of the most promising applications of mRNA technology in cardiovascular diseases is protein replacement therapy. Instead of administering therapeutic proteins directly for treatment, mRNA drugs provide genetic codes for protein production by cells only temporarily. It allows overcoming a number of disadvantages related to conventional protein treatments, including short half-life, need for repeated administration, and difficulties in manufacturing (Pardi et al. 2018). Apolipoprotein A-I (ApoA-I) is the major protein of high-density lipoprotein and is involved in reverse cholesterol transport; it has been investigated as a therapeutic target in atherosclerosis. But supporting evidence for the biological importance of ApoA-I is different from the supporting evidence for therapeutic efficacy after giving ApoA-I mRNA. While expression of ApoA-I by mRNA could be a protein replacement therapy, clinical benefits of such approach, or its effects on atherosclerotic plaque burden, have yet to be demonstrated in humans. Therefore, ApoA-I mRNA is a research tool and not a proven anti-atherosclerotic therapy. Another promising therapeutic protein is vascular endothelial growth factor (VEGF). It contributes to the process of angiogenesis, or blood vessel formation. After myocardial infarction or ischemic injury, VEGF helps increase the flow of blood into injured tissue, thus accelerating cardiac recovery. Studies have

shown that mRNA-mediated VEGF expression increases the number of blood vessels and improves heart function after injuries (Zangi et al. 2013). There are other proteins that participate in tissue repair processes, anti-inflammatory signaling, and cholesterol metabolism.

Targeting Lipid Metabolism

Lipid metabolism is a valuable target for the treatment of atherosclerosis and coronary artery disease. The low-density lipoprotein cholesterol (LDL-C) level in the bloodstream is controlled by proprotein convertase subtilisin/kexin type 9 (PCSK9) which facilitates the destruction of LDL receptors (Lagace et al. 2006) in the liver. Blocking PCSK9 increases the number of LDL receptors available to remove LDL-C from the blood.

It is important to remember that there are several molecular technologies to target PCSK9. Inclisiran is a small interfering RNA (siRNA) therapeutic which lowers hepatic PCSK9 production by RNA silencing. In two phase 3 clinical trials, LDL-C levels were significantly lowered in patients with high LDL-C with the use of inclisiran (Ray et al. 2020). Inclisiran is not an mRNA therapeutic since it is not an exogenous mRNA therapeutic protein, but instead it inhibits the translation of endogenous PCSK9 mRNA. Monoclonal antibodies and experimental vaccination strategies that try to induce antibodies against PCSK9 are other ways of inhibiting PCSK9. The mechanisms used in these approaches are different from those used for therapeutic mRNA delivery and cannot be equated with proven mRNA-mediated PCK9 suppression.

In principle, mRNA platforms could be used to encode proteins or antibody-based agents which modify lipid metabolism, but are not yet being used to directly regulate PCK9 for atherosclerosis. Additional research is needed to see if such delivery systems can be made effective, sustainable, and safe for delivery to specific tissues.

Anti-inflammatory mRNA Therapies

Inflammation is one of the major factors behind the development and progression of atherosclerosis, and thus serves as a potential target for mRNA treatments. The anti-inflammatory mRNA treatments are expected to introduce genetic code that would allow the body to synthesize proteins, which would suppress vascular inflammation. While traditional anti-inflammatory medications usually inhibit the activity of inflammatory mediators, mRNA treatments are aimed at suppressing the production of such proteins (Pardi et al. 2018). A potential approach could be the delivery of anti-cytokines such as interleukin - 10 (IL-10). Interleukin-10 is vital in the inhibition of inflammation by suppressing the generation of pro-inflammatory cytokines as well as the activation of macrophages and T cells. Elevated levels of IL-10 have been shown to reduce the amount of plaque buildup and improve the stability of plaques in cases of atherosclerosis (Moore et al. 2013). mRNA therapies encoding IL-10 may eventually help limit chronic vascular inflammation and slow disease progression. The modulation of the phenotypic status of macrophages is another approach that has been identified. There are various phenotypic statuses of macrophages; these include M1 phenotypes, which are pro-inflammatory, and M2 phenotypes, which

are anti-inflammatory (Murray 2017). Experimental mRNA strategies may be investigated for modulating macrophage inflammatory phenotypes, creating a more protective immune environment within atherosclerotic plaques. The M1 macrophages play a role in the development of the plaques because they produce inflammatory cytokines. On the other hand, M2 macrophages facilitate tissue repair and inflammation resolution. mRNA-based approaches can be used to induce a shift from the M1 phenotype to the M2 phenotype.

Post-Ischemic Angiogenesis and Myocardial Repair

Promoting angiogenesis and repair of ischemic myocardial injury is one of the important but distinct applications of cardiovascular mRNA therapeutics. These treatments are not designed to change the build-up of atherosclerotic plaques, but are aimed at enhancing vascularisation and functional recovery in tissues that are poorly vascularised.

Angiogenesis is regulated by a number of different factors, but one important factor is vascular endothelial growth factor A (VEGF-A). Preliminary tests in animal models have shown that the modified mRNA carrying the sequence of the gene for VEGF-A can be used to induce the formation of new blood vessels after a heart attack. Zangi et al. (2013) showed that the expression of VEGF-A induced by modified mRNA induced vascular regeneration and affected the responses of cardiac progenitor-cells in experimental models.

Some preliminary evidence for the feasibility and tolerability of localized VEGF-A mRNA administration was provided by subsequent human studies, including the phase 1 study reported by Gan et al. (2019) and the EPICCURE phase 2a study reported by Anttila et al. (2023).

However, these studies are mainly related to therapeutic angiogenesis and myocardial and peripheral tissue perfusion. They do not have any regression of atherosclerotic plaques, suppression of plaque-associated inflammation, or prevention of coronary atherosclerosis. Thus, post-ischemic cardiac regeneration needs to be viewed as a related, but mechanistically different application of cardiovascular mRNA therapy.

IMMUNE MECHANISMS OF MRNA-BASED CARDIOVASCULAR THERAPIES

Innate Immune Activation

The activation of the innate immune response is vital for the efficiency of the therapy using mRNAs in AS and CAD. The innate immune system recognizes the presence of the foreign genetic substance via the action of pattern recognition receptors, such as Toll-like receptors (TLRs). The artificial mRNA may be identified by TLR3, TLR7, and TLR8, which are special receptors recognizing RNA molecules and provoking immune reactions (Karikó et al. 2005). The activation of those receptors triggers cellular signal transduction resulting in the synthesis of pro-inflammatory cytokines and type I interferons. Although the induction of innate immune responses can increase vaccine efficacy, overstimulation of innate immunity

can lead to inflammatory reactions and reduction in protein expression, along with an increase in the rate of mRNA degradation. In order to tackle this issue, the advanced mRNA vaccines utilize chemical modifications, including pseudouridine and N1-methylpseudouridine, that prevent the recognition of mRNA by TLRs and thus enhance the stability of mRNA molecules along with translation efficiency (Karikó et al. 2005).

Adaptive Immune Responses

There are also mRNA therapeutics that have the ability to regulate adaptive immune responses. These include antigen-specific T and B cells, in which case, after cell uptake and translation of the mRNA, the protein encoded by the mRNA is then processed and presented through MHC molecules, thus making the immune system recognize the targeted antigen. This could help either activate or regulate the T cells depending on the purpose of the treatment. T-cell modulation has an important role to play in the development of atherosclerosis since the inflammatory Th1 T cells cause the advancement of plaques while Tregs have a role to play in suppressing vascular inflammation. mRNA-based therapy can be used to ensure that there are favorable immune responses while minimizing inflammatory responses (Lecis et al. 2023). Moreover, antigen presentation causes B cells to generate antibodies to specific antigens such as PCSK9 or oxidized LDL. Such antibodies will help lower the amount of cholesterol in the body (Moreno-Gonzalez et al. 2023).

Immune Tolerance Induction

Among the objectives in the development of mRNA therapy for AS and CAD is the production of antigen-specific immune tolerance. Unlike conventional vaccines that strive to enhance immune response, therapies for tolerance induce a suppression of an immune reaction against self-antigens responsible for inflammation, as seen in atherosclerosis. Key antigens to target include Apolipoprotein B (ApoB) and oxidized low-density lipoprotein (Raposo-Gutiérrez, Rodríguez-Ronchel, and Ramiro). Antigen-specific tolerance induction methods are based on introducing mRNA encoding disease-associated antigens in a way that induces regulatory immune reactions as opposed to inflammatory reactions. Such an approach could potentially promote regulatory immune responses, but requires validation in atherosclerosis models. Examples of such cytokines include interleukin-10 and transforming growth factor-beta (Lecis et al. 2023). Through inhibition of the activity of inflammatory T-cells, restriction of activation of macrophages, and facilitation of regulatory immune processes, the antigen-specific tolerance approach might influence plaque-associated inflammation, although direct evidence of plaque stabilization remains insufficient. The capability of mRNA systems to accurately control the process of antigen expression makes them very suitable for creating future immunotherapy methods aimed at treating cardiovascular diseases. The precise regulation of antigen presentation by mRNAs can make these technologies useful for designing novel immunotherapy approaches for heart diseases. With ongoing research, induction of immune tolerance might become an essential approach for both prevention and treatment of atherosclerosis without inducing general immunosuppression (Hansson and Nilsson 2020).

CURRENT CLINICAL TRIALS AND TRANSLATIONAL PROGRESS

Various mRNA therapies for cardiovascular diseases are under investigation via preclinical testing and clinical trials.

Table 1. Evidence-classification table distinguishing human clinical studies, preclinical findings, and conceptual approaches

Strategy	Evidence level	Appropriate interpretation
VEGF-A mRNA after cardiac ischemia/CABG	Early human clinical study	Feasibility and preliminary safety
VEGF-A mRNA for local skin perfusion	Human phase 1 study	Local protein expression and transient perfusion
ApoB peptide vaccination	Preclinical anti-atherosclerotic research	Not direct evidence for an mRNA vaccine
ApoB-encoding tolerogenic mRNA	Proposed application	Requires direct validation in atherosclerosis
IL-10 mRNA for plaque inflammation	Investigational concept in this review	No established human plaque efficacy
mRNA-mediated macrophage reprogramming	Experimental research direction	No established clinical plaque-stabilizing effect

Personalized atherosclerosis mRNA vaccines	Conceptual	No demonstrated human clinical efficacy
Inclisiran	Human phase 3 trials	siRNA, not therapeutic mRNA

The maturity of these strategies varies widely from clinical to non-clinical. Human mRNA studies of VEGF-A offer early proof of localised expression and tolerability of this protein; potential immunomodulatory role in atherosclerosis needs to be further validated in both preclinical and clinical studies. The therapeutic mRNA efficacy cannot be concluded from evidence from peptide vaccination, cytokine biology, or from any other RNA modalities.

The majority of research work is related to angiogenesis, myocardial healing, protein replacement, and treating diseases like atherosclerosis and hypercholesterolemia. Despite some mRNA strategies moving to the clinical trial phase, the majority of atherosclerosis therapies remain experimental (Zhou et al. 2026).

The EPICCURE trial (NCT03370887) is one of the key clinical trials of mRNA therapy for cardiovascular applications, a randomized, double-blind phase 2a clinical study of a chemically modified mRNA encoding vascular endothelial growth factor A (VEGF-A) in CABG (coronary artery bypass grafting) patients. The study included 11 patients with left ventricular systolic dysfunction (LVSD), seven of whom were treated with AZD8601 and four were treated with placebo. Targeted delivery of the investigational treatment was via direct epicardial injection into ischemic but viable myocardial regions. No deaths or serious treatment related adverse events were reported during the 6 months post follow-up. Data from exploratory studies indicated some benefit with regards to selected cardiac function and patient-reported outcomes but were not definitive due to the small sample size (Anttila et al. 2023).

Other human evidence is from a phase 1 trial of modified VEGF-A mRNA intradermally administered to men with type 2 diabetes mellitus. The study showed that the VEGF-A protein was transiently expressed, and that skin blood flow was increased; the primary injection-site reactions were mild (Gan et al. 2019). The results indicate that it is possible to express therapeutic proteins locally with modified mRNA. But, both studies did not conclude that mRNA therapy lowers the amount of atherosclerotic plaque or prevents coronary events. It should also be noted that the study by Zangi et al. 2013 was a preclinical study, which gives mechanistic evidence for the modified mRNA-mediated vascular regeneration following myocardial infarction, which should be differentiated from the subsequent studies in humans.

Unlike other methods, mRNA has some strengths, including temporary protein production, rapid development, and targeting of various biological pathways (Pardi et al. 2018). However, there are already existing treatments such as statins, PCSK9 inhibitors, and siRNA treatments that block PCSK9 production and reduce levels of LDL cholesterol. Thus, mRNA treatments cannot compete with

traditional cardiovascular treatments yet and require more clinical trials to prove their efficacy. The path that mRNA cardiovascular treatments take from a laboratory to the clinic is very conservative because scientists need to demonstrate that their product is safe and effective, as well as having adequate means of delivery and manufacturing, and also long-term results. The relatively small number of studies done in the field of mRNA cardiovascular treatments is proof that more research needs to be done before this technology could be applied (Damase and Cooke 2025).

COMPARISON WITH OTHER RNA-BASED APPROACHES

There are various types of RNA- based therapeutics that may involve mRNA, small interfering RNA, antisense oligonucleotides (ASOs), and Crisp technologies. They all vary in terms of their impact on gene expression and protein synthesis. In particular, the technology of mRNA therapy delivers genetic information about the protein to the cell for its production, while siRNA and ASOs mainly focus on reducing the synthesis of proteins (Damase and Cooke 2025). In addition, the technology of siRNA involves RNA interference. It means that the siRNA interacts with the complementary messenger RNA molecules and causes their degradation in order to prevent the production of certain proteins. One of the most important examples related to the cardiovascular system is the use of siRNA to target PCSK9 and thus increase the number of LDL receptors to decrease LDL cholesterol (Damase and Cooke 2025).

Table 2. Comparison of RNA-Based Approaches

Modality	Mechanism	Example	Evidence category
Therapeutic mRNA	Produces an encoded protein	VEGF-A mRNA (AZD8601)	Human early-phase cardiovascular study
siRNA	Silences a complementary target mRNA	Inclisiran targeting PCSK9	Human phase 3 LDL-C trials
ASO	Alters RNA degradation, translation, or processing	Pelacarsen targeting apo(a)	Human clinical development

Conventional vaccine	Presents antigens to elicit or modulate immune responses	ApoB peptide vaccination	Predominantly experimental in atherosclerosis
mRNA vaccine	Delivers RNA encoding an antigen	Proposed ApoB-directed mRNA vaccine	Conceptual or early experimental for atherosclerosis
CRISPR-based editing	Modifies DNA using genome-editing machinery	PCSK9 gene-editing research	Investigational

Evidence from one RNA technology cannot automatically be extrapolated to another, because these platforms differ in molecular mechanism, biodistribution, durability, immunogenicity, and clinical maturity.

Antisense oligonucleotides (ASOs) are synthetically produced nucleic acid sequences that bind to certain RNA molecules. Depending on the particular design of ASO, there is either degradation of the particular target mRNA or modification of RNA processing and splicing. Thus, ASOs regulate the production of proteins responsible for cardiovascular diseases. Some ASOs have already entered clinical trials and have been approved by regulatory agencies; they are thus more advanced as a therapy for cardiovascular diseases than other mRNA therapies (Damase and Cooke 2025). As compared to ASOs, CRISPR-based technologies are unique in terms of their ability to edit genes at the level of DNA. With the help of guide RNA, the CRISPR-based technology locates the specific DNA sequence, after which gene editing is carried out. In the context of cardiovascular research, the CRISPR- based methods are studied for editing DNA sequences related to the process of cholesterol metabolism and cardiovascular disease development in general (Pei et al. 2024). Overall, mRNA provides transient effects, siRNA and ASOs regulate gene expression, and CRISPR- based technologies modify the genetic material. Each of these strategies offers specific benefits and drawbacks for the treatment of cardiovascular diseases in the future.

FUTURE PERSPECTIVES

Future research in mRNA therapies for atherosclerosis and coronary artery disease may include development of a more personalized and targeted therapy. Personalized mRNA vaccines might be developed according to certain antigens in the case of the disease in question to make the immune system respond to pathways associated with a particular disease (Damase and Cooke 2025). Development of mRNA technology could also help in the production of proteins in certain tissues. Development of

combination therapies might be considered another way to develop mRNA therapies. mRNA treatments might be combined with other treatment types, including statins or biologic therapies, to address various mechanisms of cardiovascular diseases, including cholesterol deposition and inflammation. Moreover, artificial intelligence can assist scientists in determining and predicting suitable antigens based on massive biological and immune data. According to recent studies, the use of computer modeling and AI can help in choosing better antigens for mRNA vaccine designs (Gu et al. 2026).

CONCLUSION

Atherosclerosis and coronary artery disease are complex cardiological diseases, involving lipid deposits, endothelial dysfunction, chronic vascular inflammation and complex immune functions. While existing therapies for lipids and inflammation have been shown to positively influence the outcome of cardiovascular disease, there remains a need and an interest in exploring other therapies that could be used alongside the main lipid- and inflammation-lowering therapies.

Messenger RNA technology allows for temporary production of encoded proteins in the inside of cells without integration. The use of RNA has evolved to include new delivery systems and modification technologies that have meant that the potential therapeutic applications have grown. In the cardiovascular field, modified mRNA coding for vascular endothelial growth factor A has been proven to be feasible and tolerable in preliminary human studies for local tissue perfusion and repair after myocardial ischemia. These results, however, are not proof of efficacy in terms of the development or progression of atherosclerotic plaques.

mRNA technology is still being investigated to be used for anti-atherosclerotic immunomodulation. The strategies are anti-inflammatory proteins, inflammation pathways, modulation of macrophages, and antigen-specific immune regulation. These ideas are supported by elements of cardiovascular immunobiology and other therapeutic platforms with mRNA-based therapeutics, but there are few direct examples of efficacy from mRNA-based interventions in human atherosclerosis.

Some of the critical challenges in translation involve targeting drug delivery to specific tissues, preventing inappropriate activation of innate immune responses, sustaining expression of therapeutic proteins, tolerance to repeated doses, therapeutic manufacturing scalability, and long-term safety. Rigorous preclinical validation, proper characterization of molecular mechanisms, and well-designed clinical trials should be the focus of future studies.

All in all, the mRNA technology could be a useful tool for cardiovascular therapies. Whether it will be used to prevent or treat atherosclerosis will rely on its ability to deliver clinically significant results, in addition to the benefits of other proven lipid-lowering, anti-inflammatory, and RNA-based treatments.

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