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Review Article

Advancements in Precision Medicine for Imaging and Pharmacotherapy in Atherosclerosis: Recent Discoveries and Emerging Technologies

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ABSTRACT

Atherosclerosis is a primary factor in many cardiovascular diseases. Current treatments lack effectiveness in reducing the risk and progression of the disease, highlighting the need for better preventive measures. Precision medicine in cardiology offers personalized and patient-centered approaches to disease prevention and treatment. Innovations like machine learning and AI-assisted therapies are being explored to combat atherosclerosis, drawing from network medicine principles. This personalized approach involves analyzing gene regulation, metabolic pathways and protein interactions through mRNA therapeutics and immunomodulation techniques. Precision medicine shows promise in cardiovascular pharmacology by enabling targeted drug delivery and minimizing side effects. The review discusses AI-assisted drug discovery tools for individualized therapy and future prospects in nucleic acid-based treatments like antisense oligonucleotide therapeutics, aptamer therapy, siRNA-mediated treatments and gene slicing in precision medicine.

Keywords: Precision medicine, Drug discovery, Artificial intelligence, Machine learning, mRNA Therapeutics.

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INTRODUCTION

Atherosclerosis is a medical condition that weakens the intimal lining of moderately and large-sized arteries. It is now recognized as an inevitable biochemical and immune-mediated inflammatory disease.[1] 85% of all cardiovascular casualties are attributable to ischemic heart illness as well as other similar ischemic incidents, which are believed to be the main consequence of the aberrant cardiac function.[2] Nearly 18.6 million preventable deaths globally are due to this medical stigma, according to the research conducted by the International burden of heart disease and risk factors analysis study revealed that approximately 523 million patients globally are suffering from cardiovascular diseases.[3] Atherosclerosis's pathology, medical care and influence in the discipline of pharmacology have been contributed significantly through developments brought about by modern health care trade. However, there are additionally numerous inquiries that have yet to be addressed.

The medical management of coronary artery disease is a complex endeavor. The current guidelines regarding therapy are unsatisfactory to establish an effective treatment plan against atherosclerosis. It might be an outcome of a complicated and multidimensional pathobiology which triggers molecular disequilibrium in coronary architecture, fatty acid alteration and immunomodulation.[4] The primary causes of atherosclerosis include the traditional risk factors such as aging, familial susceptibility of immature cardiovascular disease, hypertension, hypercholesterolemia, insulin resistance, passive lifestyle as well as emerging risk factors of genetics, variations in levels of homocysteine, C-reactive protein stages, as well as biological stress in myocardial cells. These are all thought about contemporary risk categories in connection to cellular biology.[5] The current therapeutic approaches concentrate on enhancing the metabolism of lipoprotein while regulating the progress of coronary artery disease, instead of statins, novel therapies based on cytokine-targeting pharmaceuticals (generally monoclonal antibodies) have been utilized in clinical environments.

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As prophylaxis is more favorable than trying to mitigate atherosclerotic lesions and cholesterol plaque, the development of chemo preventive techniques in atherosclerosis is also crucial. The goal of progressive cardiovascular research is to clarify more effective atherosclerosis prevention measures as well as enhanced treatment possibilities. The concepts of customized treatment and precision medicine, along with the utilization of cutting-edge drug discovery innovations like neural networks and machine learning, will be the foundations of cardiovascular research in the future. These approaches are capable of overcoming the down sides of traditional pharmacotherapy. The most contemporary chemo preventive techniques, like photodynamic therapy, nanomedicine, thernostics and Nucleic acid-based experiments.[6]

In recent years, new technologies have made a major impact on the scientific and medical science. Novel RNA classes with distinct roles and astonishing changes have been found as a result of the incredible growth of information and expertise on RNA biology. The biggest challenge is translating the vast number of basic RNA biology breakthroughs into clinical RNA-based medications. This study is starting to produce encouraging results recently. Final phases of clinical investigation are accomplished by RNA medicines and they may even get FDA authorization. The invention of messenger RNA delivery techniques and the discovery of the RNA-guided gene-editing tool Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) has also led to substantial developments in the field of RNA-therapeutics. Promising examples of emerging therapeutic categories include antisense oligonucleotides and short interfering RNAs. Before adopting RNAs in a clinical context, a number of concerns must be resolved, including immunological reactions, toxicity and intracellular transport.[6] The Review aims to present an overview of the opportunities and challenges associated with the clinical translation of RNA-based therapeutics. Specifically, we highlight the importance of non-coding RNAs in the regulation of atherosclerosis in vascular diseases and novel delivery technologies.[7]

It is important to distinguish between a numbers of treatment categories when talking about the clinical potential of innovative RNA-based techniques. RNAs can function as direct agents, to start therapeutic targets for altering illness.[8] Moreover, RNAs have the ability to mediate modifications in downstream regulatory networks in an indirect manner. RNAs can also be employed as therapeutic intervention tools. Specifically, particular target genes' mRNA levels can be modulated by the use of short interfering RNA (siRNA).[9]

ADVANCEMENTS IN PRECISION MEDICINE

Comprehensive Approaches to Cardiovascular Disease Management: Statins, Alternative Therapies and Emerging Innovations

Statins are widely prescribed for managing cardiovascular disease due to their effectiveness in both preventing and treating the condition. They primarily work by inhibiting HMG-CoA reductase, a key enzyme in cholesterol synthesis, leading to increased LDL receptor activity and reduced LDL levels. Additionally, statins offer pleiotropic effects such as vasodilation, anti-inflammatory actions and immunomodulation. Despite their benefits, statins can cause adverse effects like liver dysfunction, kidney issues and muscle problems.[10]

Other medications like fibrates, inhibitors of cholesterol absorption, PCSK-9 inhibitors and Renin-Angiotensin System (RAS) inhibitors are also used to manage cardiovascular risk factors. Fibrates lower triglycerides and raise HDL levels, while cholesterol absorption inhibitors like ezetimibe reduce intestinal cholesterol absorption. PCSK-9 inhibitors and RAS inhibitors target different pathways to regulate lipid metabolism and blood pressure, offering additional options for cardiovascular management. Inflammatory pathways, particularly those involving cytokines like IL-1β, IL-6 and TNF-α, are also being explored for potential therapeutic interventions in atherosclerosis. Agents targeting these cytokines show promise in reducing inflammation and cardiovascular events, although they may have specific side effects that need careful consideration. Exciting innovations like P-selectin targeting therapies and photodynamic therapy offer further avenues for improving vascular health and managing atherosclerosis, presenting a diverse range of options for clinicians and researchers in the field.[11]

Recent Progress in Theranostic Nanoparticles for Atherosclerosis

Atherosclerosis stands as the primary cause of cardiovascular-related fatalities, spurring the development of numerous theranostic nanomaterials over recent decades for its treatment.[4] It marks the initial stage in the progression of various cardiovascular diseases. Upon the rupture of a vulnerable atherosclerotic plaque, thrombogenic substances can disperse, leading to clot formation within blood vessels. This cascade can result in Myocardial Infarction (MI), stroke and ischemic damages.[13]

Nanocarriers contain therapeutic chemicals that are directly carried to the target region, either passively or actively targeted. When using passive targeting, highly perfusable cells are used to deliver the nanomedicine to the target spot. Active targeting involves combining nanomedicine with site-specific compounds or cell-specific targeting ligands.[14,15] Amiodarone encapsulated in liposomes was used in a trial that demonstrated improved therapeutic efficacy in hypotension along with fewer adverse effects.[16] This is a great illustration of how cardiac medication nanoformulation can help improve Atherosclerosis therapy.[17] Furthermore, liposomal vesicles that have surface charge because of their chemical makeup can be applied to molecular targets. To create liposomes with a positive charge and increased affinity, for instance, cationic lipids like Dioleoylphosphatidylethanolamine (DOPE) were utilized.

Research has demonstrated that andrographolide, a conventional but poorly soluble anti-inflammatory agent that inhibits the Nuclear Factor (NF)-κB signaling pathway, can be more effectively delivered using PEG-poly(propylene sulphide) micelles. This approach enhances the drug's efficacy by passively targeting it to the desired site.[18]

In certain studies, local administration of anti-inflammatory drugs, such as steroidal medications, has been employed to treat atherosclerotic lesions. For instance, systemic use of glucocorticoids like prednisolone can cause adverse effects, including dyslipidemia, glucose intolerance and hypertension. However, these side effects were minimized through the use of nanoencapsulated prednisolone for targeted delivery to the atherosclerotic lesion. Another research group encapsulated prednisolone phosphate in long-circulating liposomes, not only demonstrating its anti-inflammatory properties but also providing insights into atherosclerotic imaging and diagnosis. These prednisolone liposomes exhibited improved pharmacokinetics compared to the free drug in human clinical trials.[19] Furthermore, prednisolone phosphate-loaded long-circulating liposomes were shown to enhance therapeutic outcomes within two days of treatment, with effects lasting up to a week. While anti-inflammatory agents are usually administered weeks or months in advance to reduce inflammation, this formulation achieved a rapid reduction in atherosclerotic inflammation.[20] Outlines strategies for targeted and theranostic nanomedicine approaches in atherosclerosis is mentioned in Table 1.[18,20-23]

The Fundamental Perspectives, Applications and Resources of Precision Medicine in the Contemporary Healthcare Sector

Precision medicine customizes treatment approaches based on individual variations in disease susceptibility and response to medications. This term has replaced "personalized medicine," which was mistakenly thought to imply treatment tailored to a single patient. Precision medicine leverages advanced drug delivery methods and genetic profiling, earning the name stratified medicine. The concept emerged alongside the Human Genome Project, which began in 1990 and took 13 years to complete, ushering in a new era of drug discovery and molecular biology.[24] While single genes often do not precisely correlate with disease pathobiology, multiple mutations typically contribute to complex conditions, making genetics alone insufficient for accurate disease prediction. Consequently, more innovative medical approaches were needed. In 2015, President Barack Obama highlighted precision medicine in his State of the Union address, sparking a significant increase in interest and adoption. Precision medicine

Table 1: Exploring Targeted and Theranostic Nanomedicine Strategies for Atherosclerosis.

Drug/Nanocarrier	Molecular Targets	Clinical significance	Tested Doses and Route of Administration	Treatment duration	References
Andrographolide/PEGpoly(propylene sulphide) micelles.	NF-κB signaling pathway.	Enhanced Delivery Efficacy.	45 μg/g micelle, 2 μg/g; andro i.v	30 days	18
Prednisolsone/Liposomes.	Atherosclerotic macrophages.	No discernible anti-inflammatory efficacy observed.	1.5 mg/kg; i.v	10 days	19
IL-10/Arginylglycyl aspartic acid conjugated pluronic-based nanocarriers.	Atherosclerotic plaque.	Capable of impeding the advancement of atherosclerotic plaques.	1.05 mg of NC with 5 μg IL10; i.v	1-3 weeks	20
Fumagillin/Paramagnetic nanoparticles.	Endothelial $\alpha v\beta_3$ integrin.	Quantification and inhibition of angiogenesis.	1.0 mL/kg; i.v.	2-4 hr	21
PLGA nanoparticles.	Plaque-targeted peptides PP1 and cRGD.	Management of advanced atherosclerotic plaques encompassing diagnosis and therapy.	-----	6 hr	23, 24

now integrates various predictive techniques, including omics, pharmaco-omics, big data, AI, ML and environmental, social and behavioral factors, aligning with public health and preventive medicine.[25]

Advancements and Challenges in RNA-Based Therapeutics: Unlocking Potential for Precision Medicine in Atherosclerosis

RNAs offer significant therapeutic benefits due to their unique biochemistry, including modifying the "unhackable" human genome, regulating gene expression and targeting epigenetic processes. However, challenges such as susceptibility to endonucleases, potential immune responses and limited cellular uptake hinder current RNA-based techniques.[26] Recent research has focused on addressing these challenges, such as replacing early phosphodiester linkages with a phosphorythioate backbone in single-Stranded Antisense Oligonucleotides (ASOs) to enhance stability, cellular absorption, bioavailability and pharmacokinetics. ASOs, particularly those with 2′ alterations, show improved binding affinity for mRNA targets and can penetrate cells efficiently.[27] Combining ASOs with cell-type-specific targeting domains, like the N-acetylgalactosamine (GalNAc) ligand for hepatocyte-specific delivery, enhances targeted distribution. Additionally, Locked Nucleic Acids (LNAs) in ASOs demonstrate strong mRNA target affinity and resistance to degradation, with mixmers and gapmers offering distinct mechanisms for inhibiting protein translation and mRNA expression.[28] These advancements, including FDA-approved RNA medications like gapmers, represent significant progress in overcoming barriers to effective RNA-based therapies.

RNA has emerged as a crucial focus in the search for new therapeutic targets, thanks to advancements in understanding messenger RNA's (mRNA) structure and function. Once viewed solely as a bridge between DNA and proteins, RNA is now recognized as a dynamic gene regulator with transformative potential.[29] This shift has expanded therapeutic possibilities across infectious diseases, cancer, neurological disorders and more recently, cardiovascular conditions, leveraging DNA- and RNA-based medicinal products to manipulate RNA molecules. The primary therapeutic approaches targeting RNA regulation of gene and protein expression include Antisense Oligonucleotides (ASOs), small interfering RNAs (siRNAs) and microRNAs.[30] However, significant obstacles must be overcome, including antigenicity, limited binding affinity and tissue transport, instability and off-target toxicity, before these therapies can become viable medicines. Current research is actively exploring the reliability and efficacy of RNA therapeutics in clinical scenarios such as familial hypercholesterolemia, insulin resistance, hypertriglyceridemia, coronary amyloidosis and atrial fibrillation, aiming to address the persistent challenge of cardiovascular diseases as a leading global cause of mortality.[31]

Advancements in Gene Expression Modulation for Atherosclerosis Treatment: Exploring ASOs and siRNAs

Antisense Oligonucleotides (ASOs) represent a fascinating class of synthetic molecules designed to alter gene expression by specifically binding to target mRNA through Watson-Crick base-pairing, thereby inhibiting translation. They target various nucleic acids like pre-mRNA, mRNA and non-coding RNA within cells, functioning based on their chemical composition and degree of hybridization.[32] ASOs can enhance RNAase H activity, leading to the suppression of protein translation. Chemical modifications of ASOs are feasible to improve their pharmacological and pharmacokinetic properties, addressing challenges such as nuclease degradation, low cellular uptake, inadequate binding affinity, off-target effects and toxicity.[33] The introduction of Phosphorothioate (PS) interactions in the backbone of ASOs marks the first generation of modifications aimed at overcoming these hurdles.[34]

Double-stranded RNA (dsRNA) molecules harness the natural RNA interference (RNAi) process to reduce post-transcriptional gene expression, a mechanism prevalent in eukaryotic cells. MicroRNAs and small interfering RNAs (siRNAs), small non-coding RNAs, drive this process through synthetic modifications.[35] Specifically designed siRNAs are created to suppress target gene expression, typically consisting of 19-25 base pairs. After exogenous transfection, siRNAs undergo further modifications during RNA interference. Dicer enzyme processes long siRNAs into double-stranded siRNAs of 21-25 nucleotides, recognized by the RNA-Induced Silencing Complex (RISC) and Argonaute 2 (AGO2). AGO2 separates the target mRNA, leading to its degradation while preserving the siRNA's antisense strand for precise gene silencing.[36] However, challenges such as toxicity, immune activation, delivery issues and off-target effects impede siRNA therapeutics development. Strategies like chemical modifications, hydrophobic ligands and nanoencapsulation enhance siRNA delivery, enabling systemic administration and improving stability.[37] These advancements address concerns like rapid breakdown by nucleases and pro-inflammatory responses, showcasing potential for atherosclerosis treatment.[38]

CRISPR-Cas9: Revolutionizing Gene Editing for Atherosclerosis Treatment

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) genome engineering, utilizing RNAs for therapeutic modulation, represents a sophisticated and innovative approach. Originally a defense mechanism in prokaryotes against foreign genetic elements, CRISPR/Cas systems have evolved into powerful tools for gene editing.[39] The CRISPR/Cas9 type II technology, commonly used in research, is characterized by its adaptability and simplicity. A single guide RNA (sgRNA) directs the Cas9 nuclease to target sequences, where it induces double-strand breaks that can be repaired through Non-Homologous End Joining (NHEJ), predominantly observed in mouse zygotes. This repair process often leads to nucleotide changes in targeted sequences, offering valuable insights into potential applications for treating atherosclerosis. The multiplex nature of CRISPR technology allows for simultaneous targeting of multiple genes, facilitating biallelic targeting and the study of multiple inactivated alleles in founder mice.[40] However, subsequent generations may require complex breeding schemes akin to traditional compound knockouts.[41]

AI-Powered Innovations in Cardiovascular Imaging and Atherosclerosis: Advancing Precision Medicine and Plaque Detection

Recent advancements in Artificial Intelligence (AI) have revolutionized various scientific domains, notably in medical imaging, including cardiovascular imaging for atherosclerosis. AI applications enhance clinical productivity by optimizing identification, diagnosis and therapeutic techniques. In cardio-physiology and pathophysiology, AI techniques such as picture segmentation, automated measurements and automated diagnosis have significantly improved cardiovascular imaging research.[42] AI-driven inquiries focus on plaque characterization, including vulnerable plaque detection, heart function monitoring and risk quantification. The concept of AI involves machines learning anthropomorphic reasoning through data and performing specific tasks autonomously.[43] Machine Learning (ML) is a subfield of AI that uses algorithms to extract insights from data and predict outcomes. Deep Learning (DL), a recent breakthrough in ML, uses neural networks to replicate human brain functioning, particularly in image analysis. DL's ability to extract high-level features from complex datasets makes it efficient in aiding roles like atherosclerosis imaging, where detailed analysis and pattern recognition are crucial.[44]

Atherosclerotic plaques can now be identified using various clinical imaging techniques that analyze plaque shape, content, anatomical challenges and associated risk factors. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are common noninvasive methods for diagnosing coronary plaques, assessing vascular remodeling, luminal stenosis and stratifying cardiovascular risk.[45] However, CT has limitations in detecting small lesions due to radiation exposure and spatial accuracy constraints. Artificial Intelligence (AI) has been introduced to enhance imaging precision, particularly with Optical Coherence Tomography (OCT) and Intravascular Ultrasound (IVUS), offering detailed cross-sectional views of coronary plaques. IVUS is effective in distinguishing plaque features but is costly and invasive, limiting broad population screening. OCT excels in detecting fragile fiber caps but faces challenges with tissue penetration. Innovative imaging techniques are crucial for precision medicine, leveraging AI to maximize diagnostic efficacy and accuracy with existing imaging data.[46]

Vulnerable plaque rupture is a major contributor to lethal forms of Coronary Artery Disease (CAD) and Acute Coronary Syndrome (ACS). Characteristics such as a large necrotic core, thin fibrous cap, inflammatory cell abundance and reduced smooth muscle cell proportion are indicative of vulnerable plaques. Computer-aided imaging techniques, including machine learning frameworks, have been instrumental in identifying necrotic elements in plaques using Intravascular Ultrasound (IVUS).[47] The recent innovation of Optical Coherence Tomography-Trans Femoral Catheter Angiography (OCT-TFCA) offers a promising approach to plaque assessment. Noninvasive Fractional Flow Reserve (FFR) analysis plays a crucial role in identifying high-risk plaques and understanding coronary physiology. This technique involves constructing coronary models, applying Computational Fluid Dynamics (CFD) methods and assessing pressure and flow parameters to diagnose myocardial ischemia accurately.[48] FFR, considered the gold standard for diagnosing myocardial ischemia, integrates machine learning methods to predict impairment by combining quantitative stenosis, plaque burden and myocardial quality into a comprehensive risk score. Studies have shown that this integrated approach significantly enhances the diagnosis of vascular dysfunction downstream compared to relying solely on stenosis measurements.[49]

CONCLUSION

This Review offers the most recent and cutting-edge methods for treating atherosclerosis pharmacologically and medically, including imaging of susceptible plaques. Finding effective anti-atherosclerotic medicines is still a difficult endeavor, despite tremendous progress being made in understanding the mechanisms underlying the complicated etiology and pathophysiology of atherosclerosis. The current wave of clinical breakthroughs is mostly concentrated on improving lipoprotein metabolism and changing the course of atherosclerosis. Theranostics, photodynamics and nanomedicine-which permits simultaneous therapy and characterization-were other fascinating novel technologies that indicated potential for addressing atherosclerosis and other heart-related conditions.

The field of current study has been completely encompassed by the RNA revolution and Therapeutics. It highlighted major improvements in the areas of establishing novel biological paradigms and translated medical technological in character. Through a more comprehensive understanding of the illness mechanisms, Atherosclerosis sickness was one ailment that profited from this massive study endeavor. Describing potential solutions was made easier by the discovery of underlying pathogenic mechanisms. However, years of more study will be required to overcome a number of technological constraints and reach the pinnacle of clinical translation.

A new era of therapeutic strategy referred to as "network medicine" has been created by restructuring the concept of individualized therapy. This new approach includes the analysis, imaging, characterization and integration of genetic, metabolic and epigenetic factors for the vast majority of complex diseases in order to enhance clinical utility by reducing the maximum toxic effects of traditional clinical practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FDA: Food and drug administrations; **CRISPR:** Clustered regularly interspaced palindromic repeats; **siRNA:** Short interfering RNA; **HMG-CoA:** Hydroxymethyl glutaryl coenzyme A; **LDL:** Low density lipoprotein; **MI:** Myocardial infraction; **IL:** Interleukins; **TNF:** Tunor necrosis factor; **NF:** Nuclear factor; **AI:** Artificial intelligence; **ML:** Machine learning; **DL:** Deep learning; **ASOs:** Antisense oligonucleotides; **LNAs:** Locked nucleic acids; **CT:** Computed tomography; **MRI:** Magnetic resonance imaging; **OCT:** Optical coherence tomography; **IVUS:** Intravascular ultrasound; **CAD:** Coronary artery disease; **CFD:** Computational fluid dynamics; **TFCA:** Trans femoral catheter angiography.

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