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A Comprehensive Review on Gene Therapy of Heart Disease

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ABSTRACT

Cardiovascular disorders—including ischemic heart disease, myocardial infarction, and heart failure—remain leading global health concerns, and most available treatments primarily manage symptoms rather than repair damaged cardiac tissue. Gene therapy provides a novel therapeutic strategy by introducing, suppressing, or modifying specific genes to address the underlying molecular abnormalities in heart disease. This approach aims to enhance blood vessel formation (via VEGF or FGF), improve calcium cycling (through SERCA2a or PLN modulation), reduce cardiomyocyte death (using genes such as Bcl-2 or Akt), and restore cardiac function through viral vectors (adenovirus, AAV, lentivirus) or non-viral carriers (lipid nanoparticles, polymers, exosomes). Emerging technologies such as CRISPR/Cas9 and RNA-based silencing enable precise correction of pathogenic mutations and regulation of gene expression. Although trials like CUPID and AC6 have demonstrated safety, challenges persist regarding limited delivery efficiency, immune reactions, off-target effects, and achieving long-term therapeutic expression. Current research focuses on developing improved vectors, heart-specific promoters, immune-modulation strategies, and combination therapies involving stem cells and biomaterials. Together, these advancements are bringing gene-based therapies for cardiac diseases closer to durable and clinically effective application.

Keywords; gene editing, heart failure, microRNA, nanoparticles, regeneration, cardiac, clinical translation.

INTRODUCTION

Gene therapy represents a direct application of molecular genetics to treat human diseases by modifying or regulating gene activity. Although originally envisioned for correcting inherited disorders, its translation into clinical medicine has been slower than anticipated due to challenges in delivering therapeutic genes effectively to target cells, controlling transgene expression, and managing immune responses triggered by delivery vectors. While the foundational concepts of gene therapy appeared promising, practical application revealed significant technical and biological hurdles. Nevertheless, continued advancements in molecular biology and vector engineering offer strong potential for gene therapy to become an important component of future medical treatment in CVDs[1].

Cardiovascular diseases (CVDs) remain the foremost cause of mortality worldwide and account for a substantial burden among non-communicable diseases. In recent years, gene therapy has emerged as a promising alternative to conventional treatments for various cardiac conditions. Coronary artery disease, heart failure, and arrhythmias continue to cause high morbidity despite modern pharmacologic and device-based therapies. The availability of human genomic data and the development of sophisticated gene delivery systems have equipped researchers with tools to target specific molecular pathways involved in these disorders. Early preclinical and clinical trials have demonstrated encouraging biological effects, including enhanced angiogenesis, improved myocardial contractility, cardiac repair, and arrhythmia control[2].

As understanding of the molecular mechanisms underlying heart failure deepens, gene therapy is increasingly viewed as a feasible therapeutic strategy. Heart failure stems from multiple etiologies and remains a global health problem despite current pharmacologic and device-based interventions. Gene therapy approaches aim to counteract or correct detrimental molecular processes in cardiomyocytes, and numerous preclinical studies have shown favorable results, laying the groundwork for future clinical translation[3].

Despite progress in other medical fields, no gene therapy has yet demonstrated consistent clinical benefit for cardiac conditions. Earlier cardiac gene therapy trials focusing on angiogenesis and modulation of cardiac function revealed substantial limitations, particularly in achieving efficient and targeted delivery of therapeutic genes. Continued refinement in the selection of therapeutic

targets, vector design, and clinical trial methodologies is essential for advancing the field and achieving long-term clinical efficacy[4].

METHODS AND MOLECULES OF GENE THERAPY

1. Adding a Healthy Gene (Gene Replacement) When a heart problem happens because a gene is missing or not working, doctors can add a new healthy copy. This new gene helps the heart cells work normally again. Example: Adding the VEGF gene helps form new blood vessels in weak heart areas.

2. Turning Off a Bad Gene (Gene Silencing) Sometimes a gene works too much or makes harmful proteins. Scientists can "turn off" such genes using small RNA molecules. Example: Turning off the PCSK9 gene lowers bad cholesterol and protects the heart.

3. Editing Faulty Genes (CRISPR/Cas9 Method) This is like using scissors to cut and fix the DNA directly. Doctors can remove, correct, or add parts of genes. Example: Fixing the MYBPC3 gene that causes heart muscle thickening (cardiomyopathy).

4. Making New Blood Vessels (Angiogenesis Therapy) In heart disease, blood flow often becomes poor. By adding genes like VEGF or FGF, new blood vessels can grow and improve oxygen supply to the heart.

5. Helping the Heart Pump Better (Calcium Handling) The heart uses calcium to beat properly. Some gene therapies help restore calcium balance. Example: The SERCA2a gene improves how heart cells use calcium, making them pump more strongly.

6. Using Stem Cells with Genes Stem cells can become new heart cells. Scientists can add helpful genes to these cells before placing them in damaged heart tissue. Example: Stem cells with the VEGF gene help repair injured heart muscle.

7. Using MicroRNAs MicroRNAs are small molecules that control many genes. Changing these can help prevent heart damage or scarring. Example: Blocking miR-21 reduces scarring in heart tissue.

8. Exosome Therapy Exosomes are tiny bubbles released by cells. They can carry helpful genes or RNA to damaged heart areas. They are safe and naturally accepted by the body.

9. Carriers Used to Deliver Genes (Vectors) AAV (Adeno-associated virus) – safely delivers genes to heart cells (AAV9) Adenovirus – works quickly but short-term (Ad5) Lentivirus – long-term delivery (HIV-based) Non-viral (liposomes, nanoparticles) – safe but less efficient[5].

METHODS AND MOLECULES OF GENE THERAPY

1. Ways to Deliver the Gene • Injection into the heart muscle (intramyocardial): directly to damaged area. • Through blood vessels (intracoronary): using a small tube (catheter). Patches on the heart: that slowly release the gene.

2. Germline Gene Therapy Involves modifying DNA in reproductive cells (sperm, eggs, or embryos). The changes are heritable, meaning they are passed to future generations. Used only in research due to ethical concerns. Example: correcting defective genes in embryos with Genetic diseases like cystic fibrosis.

3. Somatic Cell Gene Therapy Targets body (somatic) cells, so changes affect only the treated person. Safe and clinically approved for several conditions. Example: gene therapy for hemophilia or muscular dystrophy.

4. In Vivo Gene Therapy The gene is delivered directly into the patient's body using viral or non-viral vectors. Example: Luxturna (AAV-based therapy) for inherited blindness.

5. Ex Vivo Gene Therapy Cells are taken from the patient, genetically modified outside the body, and reintroduced. Common for blood-related diseases. Example: CAR-T cell therapy for cancer.

6. Viral Vector–Based Gene Delivery Viruses are engineered to deliver therapeutic genes. Types include adenoviral, adeno-associated viral (AAV), retroviral/lentiviral, and herpes simplex viral vectors.

7. Non-Viral Gene Delivery Safer methods using physical (electroporation, gene gun, microinjection) or chemical carriers (liposomes, polymers, nanoparticles) to transfer genes.

8. Gene Addition (Gene Augmentation) Introduces a functional copy of a gene to restore normal function. Example: Adding functional CFTR gene in cystic fibrosis.

9. Gene Editing Direct repair or replacement of faulty genes using tools like CRISPR-Cas9, TALENs, or ZFNs. Example: editing HBB gene in sickle cell anemia.

10. Gene Silencing Suppresses harmful gene activity using RNA interference (RNAi)orantisense oligonucleotides (ASOs). Example: Spinraza therapy for spinal muscular atrophy[6].

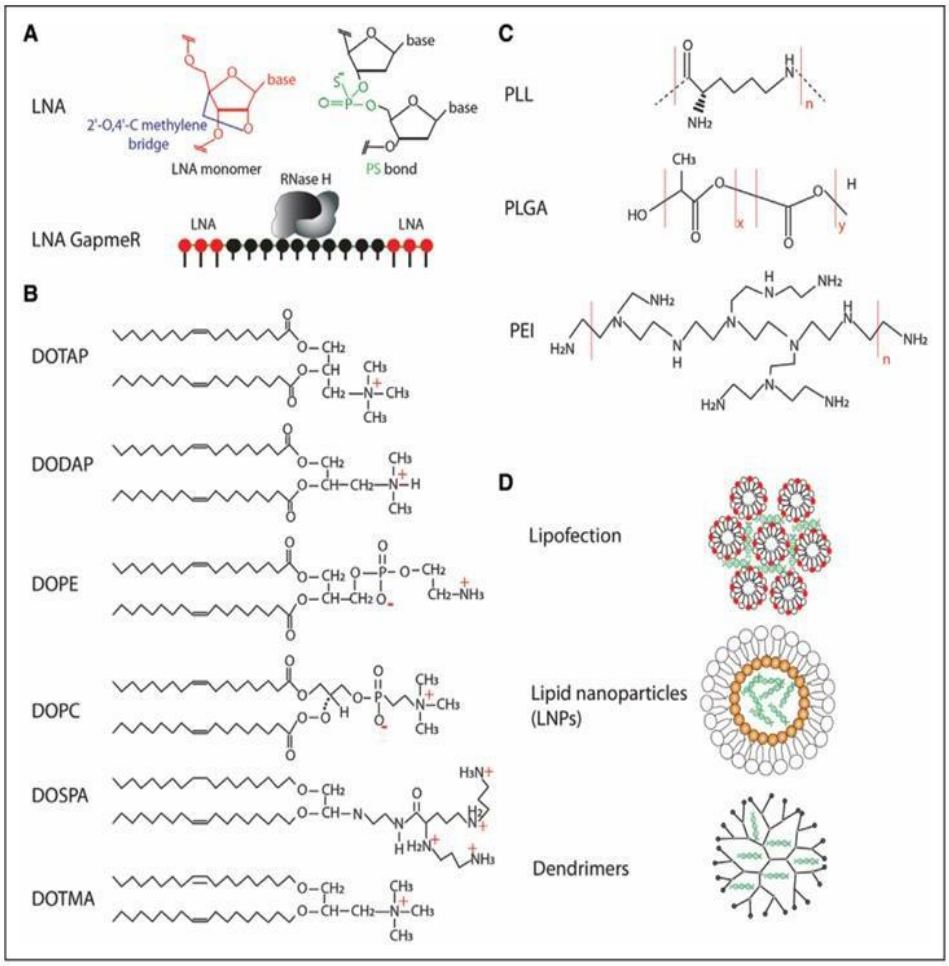

Figure 1. Molecules and methods for the delivery of RNA therapeutics.

A, Chemical structure of a locked-nucleic acid (LNA) nucleotide (upper left) and of a phosphorothioate bond (PS, upper right). The lower part of the panel shows the structure of an LNA gapmer, in which LNA-modified nucleotides are positioned at the 2 extremities of the oligonucleotide to allow RNase H accessibiltity to the central part once the duplex with the target RNA is formed. B, Chemical structure of the main cationic and neutral lipids used for lipofection and lipid nanoparticle formation. C, Main polymers used for polyplexes formation (poly(ethylenimine) [PEI], poly L-lysine [PLL], poly(lactic-co-glycolic acid) [PLGA]). D, Schematic representation of DNA-nanoparticle structures[7].

Major Problems Limiting Gene Therapy

1. Inefficient Gene Delivery

The biggest challenge in gene therapy is getting enough genetic material into the target tissue. Barriers such as the cardiac cell membrane and the dense structure of the heart make it difficult for vectors to enter cells in adequate amounts. Both viral and non-viral systems often fail to achieve high levels of gene transfer, resulting in weak or short-lived expression of the therapeutic gene[8].

2. Immune and Inflammatory Responses

Some vectors, especially **adenoviral systems**, can trigger strong immune responses. This leads to inflammation, reduced therapeutic effects, and limits how much of the vector can be safely given. Even **AAV vectors**, which are considered safer, can be recognized by the immune system, reducing their ability to persist in the body over time.[9].

3. Short-Term Gene Expression

For chronic diseases like heart failure, long-term gene expression is crucial. However, many vectors only provide temporary results. Several clinical trials—such as the **CUPID-2b trial** using SERCA2a—showed that early improvements faded because the transgene did not remain active for a sufficient duration[10].

4. Suboptimal Vector Design

Current vectors have limited tissue specificity and packaging capacity. The inability to deliver large genes or ensure precise expression in specific cell types hampers progress. Capsid engineering and promoter optimization are ongoing but remain incomplete solutions[11].

5. Biological Barriers and Disease Complexity

Organs like the heart have limited capacity to regenerate, making recovery difficult even if gene therapy is successful at the molecular level. For instance, the adult heart naturally forms very few new blood vessels, so therapies aimed at restoring circulation face obstacles. Additionally, complex diseases often involve multiple pathways, meaning a single gene may not be enough to restore function[12].

6. Clinical Trial Design and Patient Variability

Many clinical studies fail to show strong benefits because of inconsistent trial designs. Factors such as small sample sizes, wide variations in patient conditions, and lack of reliable biomarkers make results difficult to interpret. This variability can mask therapeutic benefits or create misleading outcomes[13].

7. Manufacturing, Cost, and Regulatory Challenges

Producing clinical-grade vectors is expensive and technically demanding. High manufacturing costs can make treatments unaffordable, as seen with therapies like Glybera, which was withdrawn despite being effective. Additionally, regulatory approval for gene therapies requires extensive safety testing, lengthening development time and increasing cost[14].

Vectors Used in Gene Therapy

1. Viral Vectors

Viral vectors are modified viruses that have evolved natural mechanisms to insert their DNA or RNA into host cells, making them highly efficient tools for gene delivery when engineered for safety. Among these, **adenoviral (Ad) vectors** are based on double-stranded DNA and can infect both dividing and non-dividing cells, achieving high transduction efficiency. They were among the earliest used in cardiovascular gene therapy trials, such as those delivering the *VEGF* and *SERCA2a* genes. However, adenoviral vectors tend to provoke strong immune and inflammatory responses, leading to short-lived gene expression[15].

Another important system is the **adeno-associated virus (AAV)**, which carries single-stranded DNA. AAVs exhibit low immunogenicity and can provide long-term gene expression in humans, making them among the safest and most effective viral vectors. Their primary limitation lies in their small packaging capacity (around 4.7 kb) and the presence of neutralizing antibodies in some patients. AAV vectors have been successfully used in approved therapies such as *Luxturna* for RPE65-related blindness and *Zolgensma* for spinal muscular atrophy, as well as in heart failure studies like the *CUPID* trials[16].

Retroviral and lentiviral vectors, which deliver RNA that is reverse transcribed into DNA within the host cell, enable stable gene integration into the host genome, ensuring long-term expression. However, they pose the risk of insertional mutagenesis and are mainly limited to infecting dividing cells (except lentiviruses). These systems were used in early gene therapy trials for disorders like *ADA-SCID* and *X-SCID*[17].

The herpes simplex virus (HSV), which carries double-stranded DNA, offers a large transgene capacity of up to 30–40 kb and shows strong tropism for neurons. Despite this advantage, HSV- based systems are complex to design and can trigger immune responses, confining their use mainly to neurological gene delivery research. Similarly, **baculoviruses**, though non-replicative in mammalian cells and considered safe, provide only transient expression and low in vivo efficiency, limiting them to experimental use for large-gene delivery[18].

2. Non-Viral Vectors

Non-viral vectors offer an alternative approach that prioritizes **safety, scalability, and ease of production** over delivery efficiency. These systems avoid the risks associated with viral vectors, such as immune reactions or insertional mutagenesis, but generally achieve lower transfection rates and shorter gene expression durations[19].

The most straightforward form is **plasmid DNA**, which can be injected directly or complexed with other materials. Plasmid delivery is simple, safe, and low-cost, but suffers from poor in vivo uptake. Early angiogenesis trials using *VEGF* plasmids in cardiac tissues (e.g., EUROINJECT-1 and KAT studies) demonstrated low transfection efficiency and limited clinical benefit.[20]

Liposomes and lipid nanoparticles (LNPs) encapsulate DNA or RNA molecules within lipid vesicles, allowing non-immunogenic and scalable delivery. These have found success in mRNA vaccines, siRNA therapeutics, and emerging cardiac gene therapy models. However, they face limitations in targeting precision and often result in transient gene expression.[21]

Polymeric nanoparticles, made of materials such as polyethylenimine (PEI), chitosan, or dendrimers, can be tailored for specific chemical and biological properties. Although versatile, they may exhibit cytotoxicity at high concentrations. Additionally, several **physical delivery methods**—including electroporation, ultrasound-mediated sonoporation, and gene gun delivery—can facilitate localized gene transfer without the use of biological vectors, though they are often limited by poor tissue penetration and potential cell damage[22].

3 Key Trends and Innovations

Recent research emphasizes **hybrid systems** that merge the efficiency of viral vectors with the safety of non-viral approaches, such as liposome-encapsulated AAVs. Another active area is **capsid engineering**, where new AAV serotypes (like AAV9 and AAV-SASTG) are designed to improve cardiac tissue selectivity and transduction efficiency . Advances in **promoter optimization** now allow for precise gene expression control using tissue-specific or synthetic promoters. Meanwhile, the field is rapidly transitioning toward **RNA-based therapeutics**, including microRNA (miRNA), small interfering RNA (siRNA), and CRISPR/Cas9 technologies, which enable modulation or correction of disease genes rather than simple addition[23].

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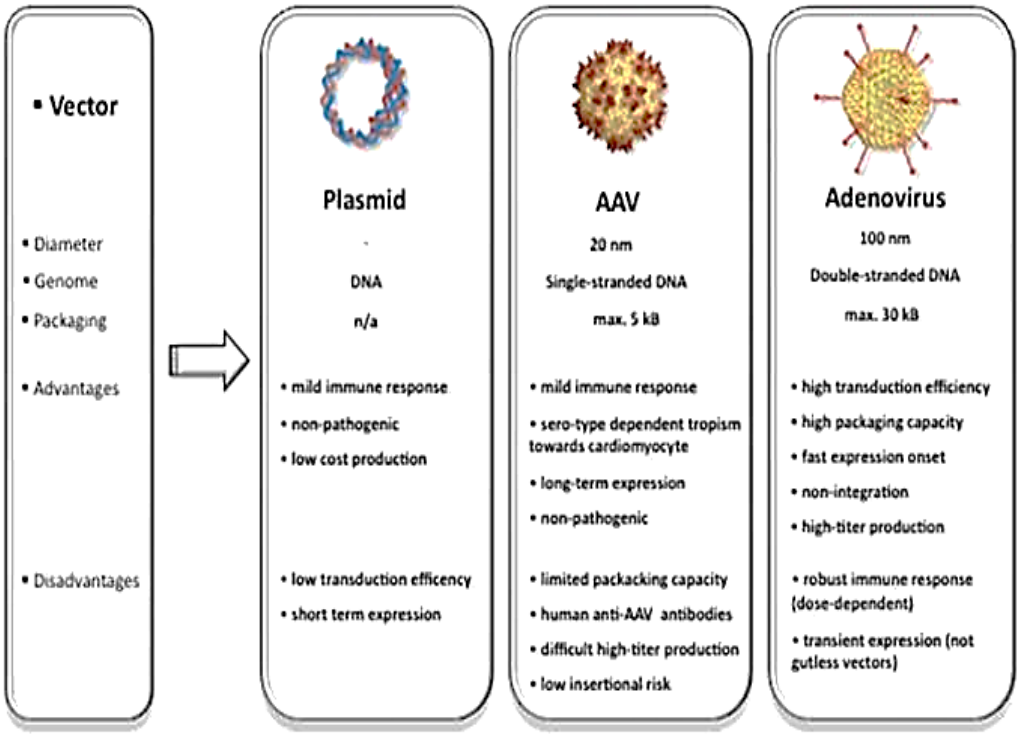

Figure 2. Vectors commonly used in cardiovascular gene transfer and specific characteristics.

To date, naked plasmid DNA, adeno-associated viruses (AAV), and adenovirus are used in 18.2%, 5.2%, and 23% of 1.902 registered gene therapy clinical trials (see www.abedia.com/wiley/vectors.ph for continous update).

Major Clinical Trials in Gene Therapy

Gene therapy has evolved over the past three decades from a theoretical concept to an applied medical reality. Initially, research centered on monogenic disorders, but significant efforts have also targeted cardiovascular and ischemic diseases. While some therapies such as *Luxturna* and *Zolgensma* have achieved regulatory approval and clinical success, most cardiovascular applications have not yet produced consistent results. This limited progress can be attributed to challenges in gene delivery efficiency, vector design, and biological complexity, as discussed[24].

A number of important clinical trials in cardiovascular gene therapy have been conducted to evaluate safety and efficacy. The VIVA trial (1999) was one of the earliest, using the recombinant VEGF-A165 protein to promote therapeutic angiogenesis in ischemic heart disease. However, it failed to demonstrate significant improvement in exercise tolerance or myocardial perfusion. Similarly, the KAT Trial (Kuopio Angiogenesis Trial, 2002) used VEGF165 plasmid DNA to induce new blood vessel formation in coronary artery disease but showed only transient effects without measurable long-term benefit. The EUROINJECT-1 trial (2005), which also employed VEGF-A165 plasmid for severe ischemic heart disease, yielded comparable results with no significant functional improvement[25].

The AGENT trials (2000–2006), which tested an adenoviral vector carrying the FGF-4 gene (Ad5FGF-4) in patients with angina and myocardial ischemia, initially confirmed safety but were halted in phase III due to lack of clinical efficacy. Likewise, the BIOBYPASS/REVASC trial (2003) used an adenoviral VEGF121 vector to promote coronary angiogenesis but achieved only modest left ventricular improvement without consistent perfusion gains (*Cannatà et al., 2020*). A more recent effort, the CUPID and CUPID-2b trials (2011–2015), investigated the delivery of the *SERCA2a* gene via an AAV1 vector for chronic heart failure. These studies demonstrated safety but failed to improve survival or symptom scores[26].

The AC6 gene therapy trial (2016) tested adenylyl cyclase type 6 delivered via an adenoviral vector in patients with heart failure, showing short-term enhancement in contractility but limited long-term effects. The NOVA trial (2003), based on AdVEGF121,

was terminated early due to inefficacy and sponsor withdrawal, while the FIRST trial (2002), which used recombinant FGF-2 protein for coronary artery disease, confirmed safety but did not achieve major clinical improvements[27].

Beyond cardiovascular disease, several gene therapy trials have transformed the treatment landscape for other conditions. For example, the ADA-SCID trial (1990–1995) used a retroviral vector to introduce the *ADA* gene into hematopoietic cells, restoring immune function in children with severe combined immunodeficiency—this became the foundation for *Strimvelis*, approved in 2016. The LCA2 (Luxturna) trial utilized an AAV2 vector to deliver the *RPE65* gene to retinal cells, improving vision in patients with Leber congenital amaurosis and earning FDA approval in 2017. Similarly, Zolgensma, which employs an AAV9 vector to deliver the *SMN1* gene, became the first curative one-time treatment for spinal muscular atrophy and was approved in 2019. Trials for Hemophilia B (AMT-060 and AMT-061) using AAV5 vectors encoding Factor IX have demonstrated long-term, stable FIX expression and reduced bleeding frequency, leading to approval in 2022. Another milestone was Glybera, an AAV1-based gene therapy for lipoprotein lipase deficiency, which was approved in 2012 but later withdrawn due to high cost and limited demand[28].

Second, short duration of transgene expression continues to limit effectiveness in chronic diseases. Third, immune responses—particularly with adenoviral vectors—have led to inflammation and loss of efficacy. Moreover, trial design challenges, including small sample sizes and heterogeneous patient populations, have made it difficult to assess true clinical benefits. Finally, economic and regulatory barriers persist, as demonstrated by the withdrawal of otherwise effective but cost-prohibitive therapies such as *Glybera*. The future of gene therapy trials now depends on the development of next-generation vectors such as engineered AAV variants (AAV9, AAV-SASTG), synthetic promoters, and gene-editing tools like CRISPR/Cas9 and siRNA technologies. These innovations aim to overcome delivery inefficiencies and achieve tissue-specific, long-term gene expression. Emerging strategies combining gene therapy with cardiac regeneration and RNA-based modulation hold great promise for future cardiovascular applications[29].

In conclusion, while gene therapy has achieved groundbreaking success in rare genetic disorders, translating these achievements to complex cardiovascular diseases remains a challenge. The lessons learned from major clinical trials underscore the necessity for safe, efficient, and targeted gene delivery systems. Continued advancements in AAV engineering, vector optimization, and RNA therapeutics are expected to bridge the gap between laboratory success and clinical applicability, paving the way toward more effective and accessible gene therapy treatments in the near future[30].

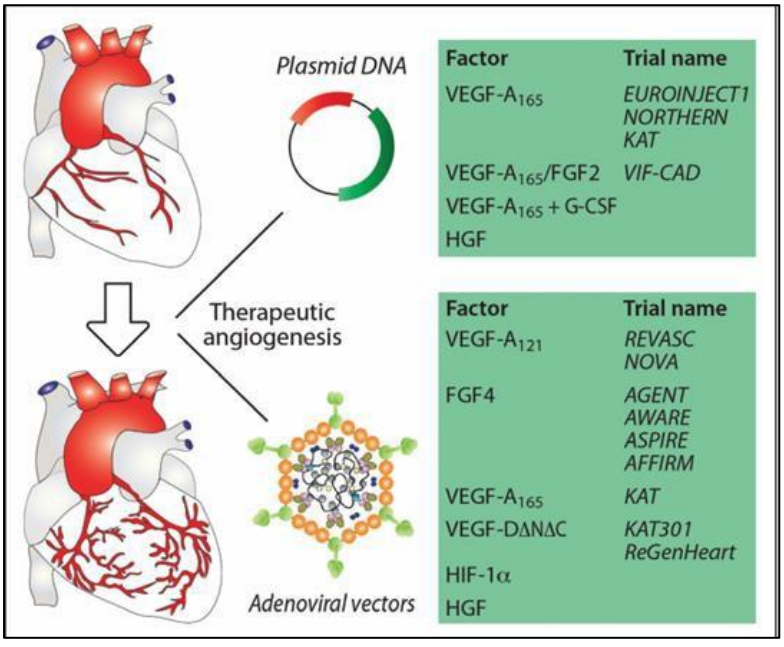

Figure 3. Clinical trials for therapeutic angiogenesis.

Th e figure summarizes the main clinical trials for therapeutic angiogenesis, grouped according to the delivery method used (naked plasmid DNA, top or adenoviral vectors, bottom), along with the indication of the therapeutic gene and the trial name. VEGF-A indicates vascular endothelial growth factor-A.

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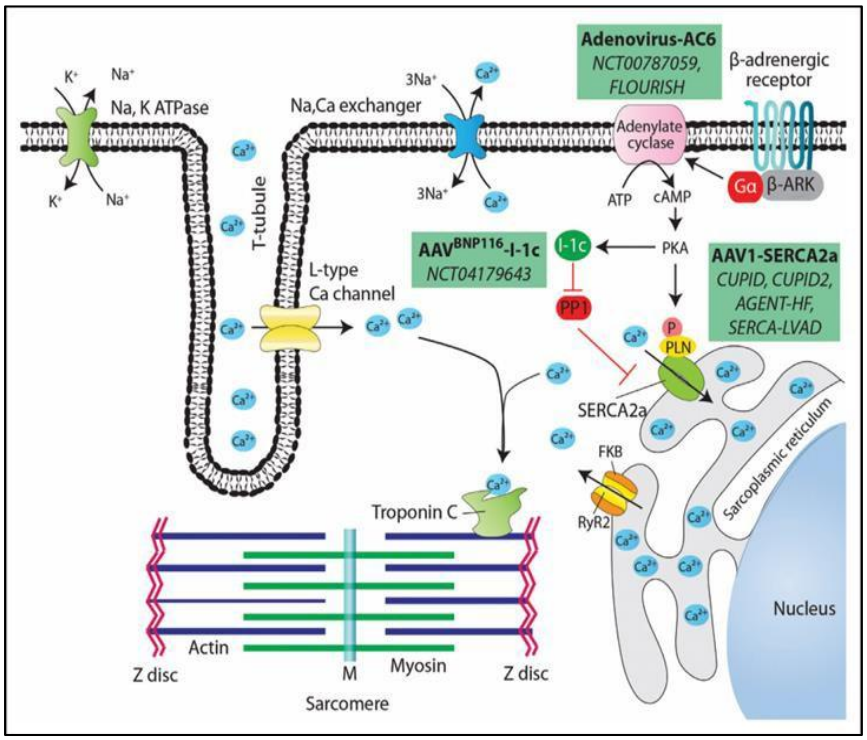

Figure 4. Clinical trials for heart failure.

The figure shows 3 current gene therapy approaches targeted to cardiac excitation-contraction coupling through the cardiomyocyte Ca2+ cycle. The depolarization of the cardiomyocyte plasma membrane induces the opening of membrane L-type voltage-dependent Ca2+ channels, with permit entry of a small quantity of Ca2+ into the cytosol; this in turn determines release of Ca2+ from the sarcoplasmic reticulum stores through the RyR2 ryanodine receptor. Massive entry of Ca2+ into the cytosol triggers biochemical coupling between actin and myosin, which is mediated by Ca2+ binding to troponin C, and subsequent contraction. In the relaxation phase, RyR2 is inhibited by the FKBP12.6protein. The released Ca2+ is in part re-convoyed into the sarcoplasmic reticulum by the ATPase SERCA2a, and in part eliminated outside the cell by the Na+/ Ca2+ exchanger (NCX). The activity of the SERCA2a pump is controlled by association of this protein with PLN (phospholamban). In its nonphosphorylated form, PLB inhibits SERCA2a, while phosphorylation blocks this inhibition. The main kinase phosphorylating PLB in cardiomyocytes (followed by pump activation) is the cAMP (cyclic adenosine monophosphate)-dependent PKA (protein-kinase A), which is under the control of β-adrenergic stimulation. In particular, engagements of β-adrenergic receptors with their ligands activates an associated, heterotrimeric G protein, which in turn leads to activation of an AC (adenylate cyclase) located on the cytosolic side of the receptor complex, which catalyzes conversion of ATP to cAMP. This in turn activates PKA, which phosphorylates (1) the L-type Ca2+ channels, thus determining further Ca2+ entry each depolarization cycle; (2) RyR2, causing dissociation of the inhibitory protein FKB12.6; and (3) PLB, blocking its inhibitory activity on SERCA2a. These modifications amplify the efficacy of Ca Ca2+ release and re-uptake every cardiac cycle. Conversely, dephosphorylation of PLN leads to SERCA2a inactivation. This is mainly carried out by PP1 (protein phosphatase-1), which is inhibited by I-1c (inhibitor-1c). The cartoon shows the 3 main clinical approaches to modulate these pathways in heart failure by transfering the cDNAs coding for SERCA2a, AC6, or I-1c (rectangular green boxes), with the indication of the vector used and the name of the clinical studies.

Gene Delivery Techniques in Gene Therapy

Gene delivery is the central process of gene therapy—it determines how efficiently a therapeutic gene can reach target cells, express its function, and remain stable over time. As *Inder Verma* famously stated, the three main challenges in gene therapy are "delivery, delivery, and delivery." The overall success of gene therapy depends heavily on the type of vector used, the route of administration, and the biological properties of the target tissue[31].

Gene delivery methods are broadly classified into viral and non-viral techniques. Viral delivery systems use modified viruses to transfer genes into host cells. These viral vectors are engineered to be replication-defective and safe, retaining only the ability to

deliver the therapeutic gene. Among them, adenoviral vectors are the most commonly used for transient gene expression. They are introduced through direct myocardial or coronary artery injections and have been used in cardiac angiogenesis and heart failure therapy, such as with *VEGF*, *FGF*, and *SERCA2a* genes. However, adenoviral systems often trigger strong immune and inflammatory responses, resulting in short-lived expression. The adeno-associated virus (AAV) system, on the other hand, can achieve long-term expression in tissues like the heart, liver, and muscle. AAVs are typically delivered systemically or locally and have proven highly effective in treatments such as *Luxturna* and *Zolgensma*. Their major limitation is their small gene-carrying capacity (below 5 kilobases) and vulnerability to pre-existing immunity. Retroviral and lentiviral vectors work through ex vivo transduction of dividing or non-dividing cells, offering stable integration and long-term gene expression, which makes them ideal for stem-cell–based therapies such as *ADA-SCID* and *CAR- T cell therapy*. However, these systems carry a risk of insertional mutagenesis. Herpes simplex virus (HSV) vectors, which can accommodate large genes and target neurons, are used mainly for neurological gene therapy, though their production is complex and may cause immune activation. Baculoviral vectors are another option; while non-replicative in mammals and safe, they are limited by transient expression and poor in vivo stability[32].

Non-viral delivery systems provide a safer, more scalable alternative, though they generally exhibit lower transfection efficiency. These systems employ physical or chemical means to transfer naked DNA, RNA, or their complexes into cells. Plasmid DNA injection is the simplest technique, involving direct administration of naked DNA into tissues. It has been used in cardiac angiogenesis trials such as *EUROINJECT-1* and *KAT*, but it suffers from low efficiency, especially in heart muscle. Liposome-mediated systems, or lipid nanoparticles (LNPs), encapsulate nucleic acids in lipid vesicles, making them biocompatible and scalable for clinical use. They have become crucial in mRNA vaccine and siRNA delivery, and are being tested in cardiac gene regulation through microRNA delivery, though targeting precision remains limited. Polymeric systems—based on materials like polyethylenimine (PEI), chitosan, and dendrimers— can be chemically tuned for specific targets, but may exhibit cytotoxic effects at higher concentrations. In addition, physical delivery techniques such as electroporation, ultrasound- mediated sonoporation, and gene-gun delivery have been explored. These approaches rely on creating temporary pores or mechanical forces to allow DNA uptake, though they often suffer from low tissue penetration and possible cell damage. More advanced options include hydrodynamic injection, which involves rapid, large-volume DNA injection for liver or vascular targets, and nanoparticle-based systems, which use magnetic or gold nanoparticles to achieve targeted or image-guided gene delivery.The route of delivery plays a crucial role in gene therapy efficacy, particularly in the heart[33].

Intramyocardial injection provides precise, localized delivery but is invasive and limited to small tissue regions. Intracoronary infusion, often combined with balloon occlusion, is minimally invasive and clinically familiar but suffers from vector washout. Retrograde coronary venous infusion, which introduces vectors via the coronary sinus, can enhance vector retention but is technically demanding and risks venous damage. Endocardial catheter delivery, guided by imaging systems like NOGA, allows targeted and less invasive administration but requires specialized expertise. Systemic administration through intravenous or intra-arterial routes is practical for small vectors like AAV9, although it demands tissue-specific targeting to avoid unwanted gene expression in non-target organs. Several factors influence gene delivery efficiency, including vector tropism, which determines a vector's ability to target specific cell types such as cardiomyocytes (AAV9), and promoter design, where tissue-specific or synthetic promoters can enhance expression control. The dosage and exposure time also affect transduction rates, while pre-existing immune responses— particularly to AAV—can neutralize vectors and limit their effectiveness. Moreover, the disease state of the target tissue (such as fibrosis or ischemia) often reduces uptake and expression efficiency [34].

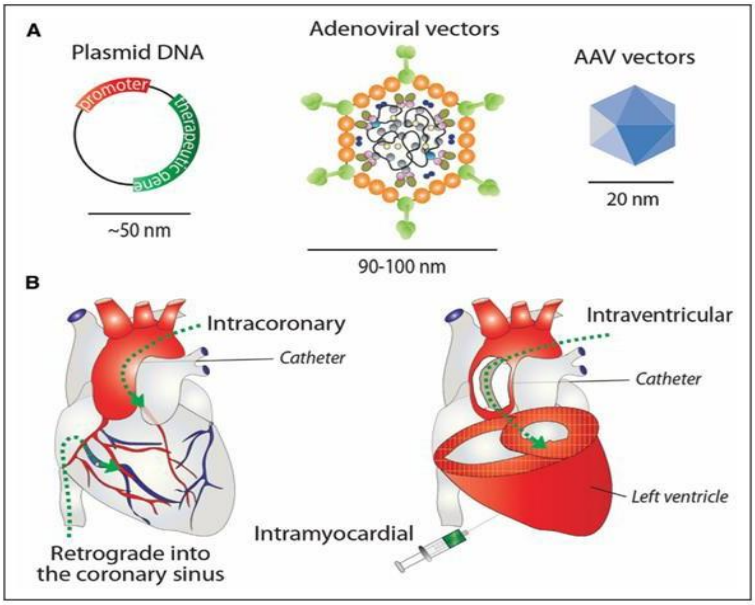

Figure 5. Delivery vehicles and routes for cardiac gene therapy

A, Schematic representation of the main delivery strategies for cardiac gene therapy (injection of naked plasmid DNA or gene transduction using adenoviral or adenoassociated virus [AAV]-based vectors). The approximate size of the delivery vehicle is indicated. B, Main delivery routes to reach the heart. These include injection into the coronary artery as during standard percutaneous coronary intervention or retrograde into the coronary sinus, on the left side panel; or intramyocardial, on the right side panel, through either direct injection after minithoracotomy or during bypass surgery, or after percutaneous catheterization to reach the left ventricle, followed by transendocardial delivery.

Recent years have brought significant innovations in gene delivery. Capsid engineering has produced AAV variants like AAV2i8 and AAV9-SASTG with enhanced heart specificity and reduced immune detection. The integration of CRISPR/Cas9 genome editing allows for precise gene correction, delivered through viral or lipid-based systems. Exosome-based delivery uses natural extracellular vesicles for safe and biocompatible transfer of RNA or DNA molecules. MicroRNA and antisense oligonucleotide technologies are also emerging, enabling gene modulation without permanent DNA integration. Additionally, magnetofection, which uses magnetic nanoparticles to direct therapeutic genes to specific organs, represents a promising, non-invasive delivery strategy.

In conclusion, gene delivery remains the most challenging and critical step in successful gene therapy. Viral vectors such as AAVs dominate current clinical applications due to their high efficiency and safety, while non-viral systems continue to improve for RNA-based and transient therapies. The future of gene therapy will depend on achieving precise targeting, avoiding immune reactions, and ensuring stable, long-term expression. Together, these innovations will expand the potential to treat complex diseases such as heart failure, muscular dystrophy, and neurodegenerative disorders.

Other Treatments for Cardiac Arrhythmias

Cardiac arrhythmias are abnormal heart rhythms that arise from irregular electrical impulses in the myocardium. These disturbances can range from benign premature beats to life-threatening conditions such as atrial fibrillation (AF) and ventricular tachycardia (VT). While gene therapy holds potential for future rhythm correction, several conventional and well-established treatments are already available and widely used in clinical practice to manage arrhythmias and prevent cardiac complications.

The first and most common method of management is pharmacological therapy, which utilizes antiarrhythmic drugs to restore or maintain normal cardiac rhythm. These drugs are categorized according to their effects on ion channels and conduction pathways. Class I agents, such as quinidine and lidocaine, act as sodium channel blockers; Class II agents are beta-blockers like metoprolol and propranolol; Class III drugs, including amiodarone and sotalol, block potassium channels; and Class IV agents, such as verapamil and diltiazem, inhibit calcium channels. Additional drugs like digoxin and adenosine are also used for specific types of arrhythmias. Pharmacologic therapy is non-invasive and effective for rate and rhythm control, though it carries risks such as proarrhythmia, drug interactions, and systemic toxicity, particularly with long-term use of agents like amiodarone.

Another widely used treatment is electrical cardioversion, which delivers a synchronized electrical shock to reset the heart's rhythm to normal sinus rhythm. It is frequently employed for atrial fibrillation, atrial flutter, and ventricular tachycardia without pulse. This technique provides rapid restoration of rhythm but requires anesthesia and carries a small risk of thromboembolism. Catheter ablation represents a more modern, minimally invasive approach in which radiofrequency or cryoenergy is used to destroy small regions of heart tissue responsible for abnormal electrical circuits. It is highly successful for supraventricular tachycardia (SVT), atrial fibrillation, and ventricular tachycardia, offering long-term control with minimal recurrence, though it carries procedural risks such as vascular injury or heart block.

For patients with dangerous or recurrent arrhythmias, implantable cardioverter-defibrillators (ICDs) play a vital role. These devices continuously monitor cardiac rhythms and deliver electrical shocks to terminate life-threatening arrhythmias like ventricular fibrillation or ventricular tachycardia. ICDs are especially useful in post-myocardial infarction patients or those with heart failure at risk of sudden cardiac death. Although life-saving, they are expensive, can deliver inappropriate shocks, and may cause psychological distress in some patients. Similarly, pacemaker implantation is used to treat bradyarrhythmias and heart blocks by sending electrical impulses to maintain a regular heart rate.

Pacemakers may be single-chamber, dual-chamber, or biventricular, depending on the patient's condition. They are highly reliable but require surgical implantation and carry risks of infection or device malfunction.

In some cases, particularly in patients undergoing open-heart surgery, the surgical Maze procedure is employed. This involves creating scar lines in the atria to block abnormal electrical pathways and restore coordinated rhythm. Though effective, it is highly invasive and reserved for patients with severe or refractory atrial fibrillation.

Lifestyle modification is another important aspect of arrhythmia management. Addressing contributing factors such as excessive caffeine or alcohol consumption, sleep apnea, thyroid disorders, and stress can significantly improve outcomes. While lifestyle changes alone may not cure severe arrhythmias, they enhance the effectiveness of pharmacological and interventional treatments.

The management strategy for arrhythmias depends on their type and severity. Atrial fibrillation is typically managed with beta-blockers or calcium channel blockers for rate control, along with anticoagulants to prevent stroke. Electrical cardioversion, ablation, or Maze surgery may be considered for rhythm correction. Atrial flutter and supraventricular tachycardia (SVT) can often be treated with vagal maneuvers, adenosine, or catheter ablation. Ventricular tachycardia (VT) may respond to amiodarone or lidocaine, but ICDs or surgical interventions are often required for long-term management. Ventricular fibrillation (VF) demands immediate defibrillation to restore life-sustaining rhythm. For bradycardia and heart block, pacemaker implantation remains the standard of care, while congenital long QT syndrome and channelopathies are managed with beta-blockers or magnesium sulfate, and in severe cases, ICD implantation or left cardiac sympathetic denervation.

Looking toward the future, research is exploring biological and genetic approaches that could eventually complement or replace hardware devices. Gene therapy aims to modify ion-channel expression to stabilize electrical activity in the heart. Stem-cell therapy seeks to regenerate functional pacemaker cells to replace damaged conduction tissue. Optogenetics—an experimental approach—uses light-activated ion channels to control cardiac rhythm with high precision. Additionally, RNA-based therapies, including microRNA modulation and antisense oligonucleotides, are being studied to influence genes involved in arrhythmogenesis. These emerging strategies aim to develop biological pacemakers, providing a natural and lasting solution for rhythm correction.

In conclusion, the treatment of cardiac arrhythmias spans a wide range—from pharmacological drugs and electrical therapies to device-based and surgical interventions. While these existing approaches effectively manage symptoms and prevent sudden cardiac death, they are often limited by recurrence, side effects, and procedural risks. The integration of gene and cell-based therapies represents the next frontier in cardiology, offering the potential for permanent correction of electrical defects rather than temporary control. Future advancements in biological pacemaker development and gene modulation may revolutionize the treatment of cardiac rhythm disorders, offering safer, more durable, and personalized options for patients worldwide.

Conclusion

Gene therapy for cardiovascular disease has evolved from early experimental research into a rapidly advancing multidisciplinary science combining molecular genetics, biomedical engineering, and computational medicine. Initial studies by Baek and Khurana established proof of concept through angiogenic and anti-restenotic gene strategies using VEGF, FGF, and eNOS, while later clinical trials such as CUPID and AC6, discussed by Pleger et al., demonstrated safety but revealed persistent limitations in delivery efficiency and immune response. Cannatà et al. later identified inadequate myocardial transduction as the main obstacle, emphasizing that successful therapy depends on achieving precise, high-coverage, and targeted delivery. Recent reviews, including the 2025 Gene Therapy in Heart Disease Review and IJDDT 2024, introduce major innovations such as AAV capsid

bioengineering, extracellular vesicle and nanoparticle- based delivery, hydrogel depots, and artificial intelligence for patient stratification and dose optimization. Collectively, these works show that modern cardiac gene therapy is transitioning from gene addition toward genome editing and RNA modulation using CRISPR, siRNA, and hybrid vectors. Although immune barriers, scalability, and long-term expression remain challenges, the convergence of advanced delivery systems and data-driven design now places effective, personalized, and durable gene-based treatment for heart disease within realistic clinical reach.

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