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Somatic Gene-Editing Potential and Engineering Barriers for Chronic Cardiovascular Disease Management

Ziya Xu

Concord College, Shrewsbury, UK
mimi_7773@outlook.com

Abstract. Cardiovascular diseases (CVDs) are major chronic health conditions, and some patients require long-term medication to control disease progression and associated risks. The need for more durable treatment has therefore significantly increased, leading to importance to find a more long-lasting treatment strategy. This paper examines the potential of somatic gene editing in the foreseeable future, while evaluating the engineering challenges and ethical limitations. Current research demonstrates the potential of somatic gene editing in vivo to modify disease-associated genetic alterations, providing evidence that gene editing could contribute to more durable CVD treatment. However, off-target effects remain the main safety issue, as an accidental change to unintended DNA regions may lead to lethal biological consequences. In addition, safely and efficiently delivering editing agents is an engineering challenge, as precision and capacity have to be both guaranteed. Furthermore, there are ethical issues regarding genetic diversity and social inequalities due to a feasibility of low accessibility to gene editing therapy. Overall, somatic gene editing shows considerable potential to shift the management of selected chronic CVDs towards more durable, mechanism-based treatment, but significant engineering, safety and ethical barriers must be addressed before it can become a reliable alternative to long-term medication.

Keywords: Somatic gene editing, cardiovascular diseases, chronic disease management, dCas9-SSAP, in vivo delivery

1. Introduction

Cardiovascular diseases (CVDs) are among the leading causes of mortality worldwide, with many chronic conditions requiring long-term medication including medicines such as statins, lisinopril and metoprolol; however, this may lead to issues such as statins, lisinopril and metoprolol. Long term pharmacotherapy frequently encounters patient adherence barriers, cumulative treatment related burdens, and the inability to address underlying pathogenic mechanisms of disease. Although several types of CVDs can receive short term interventions such as surgery to substantially lower disease risk and accelerate recovery, surgical interventions carry non negligible risks of peri operative and long term complications. Therefore, somatic gene editing for curative intervention of CVDs is regarded as a potential alternative for large cohorts of CVD patients who require lifelong medication management.

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Genome editing therapy has evolved from early trial and error molecular tools into programmable, highly specific techniques capable of directly correcting disease causing DNA sequences. Initially, zinc finger nucleases (ZFNs) and TALENs were utilised for targeted DNA cleavage, laying foundational groundwork for clinical translation. Subsequently, CRISPR Cas9 systems were introduced as RNA-guided double-strand break-inducing tools, leading to FDA approvals including Casgevy for sickle cell disease. Somatic genome editing, which shares core molecular principles with CRISPR Cas9, has attracted growing research interest for cardiovascular applications. Genome editing shifts cardiovascular treatment paradigms from symptomatic phenotype management toward modification of disease-associated genetic mechanisms. In 2018, somatic genome editing with CRISPR/Cas9 was applied to correct a potentially lethal monogenic cardiac disorder [1].

Studies demonstrate that AAV serotype 9 based delivery of the SaCas9 system can specifically disrupt mutant alleles within cardiomyocytes of R176Q heterozygous mice in vivo. These preclinical findings provide proof of concept that in vivo somatic editing can modulate pathogenic cardiac genetic variants in animal models that cardiovascular gene editing is now moving from preclinical research toward clinical translation. Among relevant research directions, PCSK9 targeted gene editing constitutes a major focus. PCSK9 is an enzyme which binds to LDL receptors and increases their degradation leading to the increase in low density lipoprotein cholesterol (LDL-C) which is a key risk factor for atherosclerosis and cardiovascular events. Traditional PCSK9 inhibition is based on the continuous use of drugs. VERVE 101 is a CRISPR gene editing therapy that was characterised in 2023 by Horie and Ono for the reduction of LDL-C and PCSK9 in heterozygous familial hypercholesterolemia (HeFH) patients [2].

Despite unresolved concerns over long-term safety of VERVE 101 which has not yet been established in humans, the positive results of the initial human clinical trials demonstrate its potential use in the near future to reduce the risk of atherosclerotic disease. Gene editing therapy has great promise for treatment of CVD, but there are several non-trivial issues to consider for its practical application. First, safety is the principle for clinical gene editing, and high editing precision is essential to avoid off target events, in which unintended DNA cutting takes place at nontarget genomic sites and produces unpredictable genomic changes. Gene editing delivery systems encompass both viral and non-viral vectors. Payload capacity, vector size constraints and biosafety represent core tradeoffs for different delivery platforms. Recent research on DNA nanostructures, including DNA origami-based gene editing systems, has achieved preliminary progress for precise in vivo therapeutic delivery [3, 4]. Gene editing therapy triggers extensive ethical debate, including concerns such as potential impacts on population level genetic diversity, risks of exacerbating social healthcare inequalities, and broader questions regarding the societal role of genomic modification technologies.

Although its real-world clinical deployment remains constrained by biological and engineering obstacles, somatic gene editing offers the possibility of durable, potentially curative intervention for chronic CVDs. This paper evaluates the therapeutic potential of somatic gene editing for chronic CVDs, summarises existing preclinical and translational research progress, analyses pivotal engineering bottlenecks, explores ethical and societal constraints, and assesses whether somatic gene editing can serve as a realistic alternative to lifelong pharmacotherapy for chronic CVD conditions.

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2. Therapeutic potential and engineering challenges of somatic gene editing for chronic CVDs

2.1. Therapeutic potential of somatic gene editing

Similar to conventional gene therapy, somatic gene editing modifies DNA sequences within somatic cells to treat or ameliorate genetically driven diseases. Somatic gene editing targets diverse somatic cell populations and excludes germline cells, meaning genomic modifications are not transmitted to subsequent generations. Somatic gene editing has received clinical approval for selected therapeutic indications, enabling direct correction of pathogenic genetic mutations within diseased tissues of living individuals. Somatic gene editing carries particular promise for subsets of CVDs with well-defined genetic targets, where editing agents can be delivered to target somatic cell genomes to achieve long lasting therapeutic effects. Chronic CVDs commonly require continuous lifelong pharmacotherapy, generating sustained physical, financial and psychological burdens for patients. Current therapeutic strategies have been mainly directed towards control of pathological pathways involved in the disease processes. In contrast, a mechanism oriented, durable intervention may be possible with somatic gene editing. Such long lasting therapeutic effects may reduce patient dependence on continuous medication and create opportunities for personalised therapeutic strategies to optimise disease control.

CRISPR/Cas9 has been used to correct catecholaminergic polymorphic ventricular tachycardia (CPVT), a life threatening monogenic cardiac disorder which may lead to sudden cardiac death in young people [1]. Although beta blockers are the standard of clinical management for CPVT, they only control 30% 50% of clinical symptoms, and have significant adverse effect profiles [5]. This clinical restriction is highly in favour of permanent curative interventions. The most common type of CPVT is caused by an autosomal dominant (AD) mutation in the RyR2 gene. Experiments with RyR2 heterozygous mutant CPVT mice have shown that having RyR2 knocked down is not detrimental to the animal, and so suppression of the mutant RyR2 alleles will not cause any physiological damage. CRISPR/Cas9 was efficiently and specifically delivered in vivo using adeno associated viral (AAV) vectors, and in this model of CPVT, was successful at suppressing arrhythmogenesis. While these preclinical results confirm the potential of in vivo somatic genome editing of disease relevant cardiac mutations, success cannot be extrapolated to more complex multifactorial cardiovascular diseases, where most chronic cardiovascular diseases are caused by a combination of genetic, metabolic and environmental factors.

In addition to the inherited mutations in the germline, acquired somatic mutations play a role in the pathogenesis of CVD. These somatic genetic changes can affect the function of the cardiovascular cell, and also the progression of the disease itself. Somatic mutations occur in a specific cell/tissue population, do not pass to the germline and modify the activity of the specific subset of cells and can therefore play a role in CVD pathogenesis. Examples include somatic mutations of GNAI2, JAK2, TET2 and PH in idiopathic VT, ischemic cardiomyopathy (ICM), heart failure (HF) and pulmonary hypertension (PH) respectively [6]. This finding suggests that somatically editing pathogenic somatic mutations might provide potential therapeutic approaches and thus somatic gene editing could be a disease-modifying cardiovascular therapeutic approach. However, there is significant inter-patient variability in somatic mutation burden and significant heterogeneity in the distribution of mutated cells across different cardiac tissues means that uniform editing is still a significant challenge; only a subset of mutated cells may be edited, failing to result in a meaningful clinical improvement, and this is a largely under-appreciated limitation in current preclinical studies. Compared with conventional cardiovascular therapeutics, somatic gene editing possesses unique clinical advantages in addressing progressive and refractory chronic CVDs. Long-

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term drug intervention often suffers from gradual drug tolerance, requiring continuous dose escalation or drug replacement to maintain therapeutic efficacy, which further increases the risk of hepatic and renal metabolic damage in chronic patients. In contrast, precise somatic genomic modification can stably correct core pathogenic factors at the genetic level, fundamentally reversing abnormal cellular phenotypes and blocking continuous disease deterioration. For refractory cardiovascular diseases that cannot be effectively controlled by standardised medication regimens, somatic gene editing provides a novel intervention dimension that breaks through the ceiling of traditional symptomatic treatment. Moreover, one-time or short-term gene editing intervention can effectively avoid repeated drug exposure and frequent hospital follow-ups, significantly improving patient quality of life and reducing long-term public healthcare system expenditures caused by chronic CVD recurrence and complication management.

2.2. Engineering challenge 1: off target effects

Safety is the primary consideration for clinical gene editing, requiring minimisation of unintended DNA cleavage events. Off target genomic modification can induce unforeseen genetic rearrangements and downstream biological consequences with potentially lethal outcomes. Therefore, high editing accuracy is a necessary prerequisite for successfully achieving the clinical application of cardiovascular gene editing technology. Off-target events are not merely random genomic error cuts, as low-frequency off-target editing may accumulate over time in long-lived and low-renewal rate cardiac cells. Unlike rapidly dividing immune cells, cardiac cells persist for decades, meaning any unintended genomic alteration may remain present for the patient's lifespan, amplifying long term oncogenic or functional risk.

dCas9 SSAP, a novel gene editing tool reported in 2022, enables precise editing of long genomic sequences without inducing double strand DNA breaks [3]. Experimental data show that dCas9 SSAP produces less than 0.3% editing errors during 1 kb sequence insertion, whereas conventional Cas9 achieves comparable editing yields but carries error rates reaching 10 16%. Furthermore, dCas9 SSAP was engineered to reduce its molecular size by more than half while preserving comparable editing efficiency, facilitating packaging within AAV vectors for in vivo delivery. This engineering innovation illustrates feasible pathways toward safer genome editing platforms for future cardiovascular applications.

Although dCas9 SSAP delivers marked improvements in editing precision, it cannot guarantee complete clinical safety. Persisting safety concerns include vector mediated off target delivery to non-target somatic cells, unpredictability of long-term biological responses following genomic modification, and long-term stability of edited genomic loci. Additionally, a balanced trade off must be maintained between editing efficiency and precision to maximise therapeutic output for cardiovascular disease applications. While dCas9 SSAP avoids double strand breaks, it still carries risks of unintended sequence insertion at off target sites, and its performance may degrade within the complex chromatin environment of cardiomyocytes, where dense chromatin packing can alter the accessibility of target DNA sequences. Current characterisation of dCas9 SSAP mostly relies on cell line experiments, and real-world performance in intact cardiac tissue remains inadequately characterised.

From the perspective of cardiovascular clinical safety, the tolerance threshold for off-target editing in cardiac tissue is far lower than that in other human tissues. Minor genomic errors that are negligible in renewable tissues may trigger irreversible arrhythmia, myocardial dysfunction or even malignant transformation in permanent cardiomyocytes. Current detection technologies for off-target effects are mostly limited to short-term genomic sequencing screening, lacking long-term

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dynamic monitoring systems for edited cardiomyocytes. Such technical limitations make it difficult to fully evaluate the latent safety risks of gene editing therapy for chronic CVD treatment, greatly restricting its large-scale clinical promotion and standardised application.

2.3. Engineering challenge 2: delivery

Safe and efficient delivery of gene editing machinery to diseased cardiovascular tissues and target cell populations represents a core technical barrier. Delivery systems must reach target tissues, enter target cells, and release editing components such as dCas9 SSAP or CRISPR/Cas9. While many gene editing clinical trials adopt ex vivo editing workflows, ex vivo manipulation is incompatible with multiple cell types including haematopoietic stem cells (HSCs). Therefore, in vivo somatic editing demands high performance delivery systems to transport editing agents safely and effectively inside living organisms [7].

Viruses have evolved natural mechanisms to facilitate in vivo cellular transduction, providing attractive delivery vehicles for gene editing cargoes. Recombinant adeno associated virus (rAAV) represents a leading delivery platform for clinical gene therapy. Although CUPID I and II trials failed to produce clinically useful therapeutic improvements, the potential of rAAV based gene therapy for cardiovascular indications was underscored. Lentiviruses (LVs) constitute an alternative vector with larger cargo capacity in abundance up to 10 kb, allowing packaging of most gene editing components within a single vector. A prominent non-viral delivery vehicle are lipid nanoparticles (LNPs), which are microscopic delivery systems that have been approved for human clinical use by the FDA [8, 9]. LNPs can be used to deliver gene editing agents in vivo and have been used for other nucleic acid cargos such as siRNAs and therapeutic mRNAs. LNP cargo is delivered in the cytosol by endocytosis, where endosome acidification is responsible for LNP contents to be released [7]. Viral vectors, on the other hand, have much higher transduction efficiencies, while non-viral platforms have their own benefits such as biosafety and design flexibility but also have their drawbacks, such as less transduction efficiency and limits on payload size.

A critical shortcoming of existing vector systems lies in cardiac specific targeting. Viral and non-viral delivery agents are found to have broad tissue tropism that an editing machinery could be delivered to other organs in addition to the cardiomyocytes, such as liver and skeletal muscle. This extensive distribution causes off-target risk of editing non cardiac tissues and may decrease effective dosage to the target tissue in the diseased heart. Although vectors are able to achieve some degree of cardiac accumulation, most of the adult cardiomyocytes are post mitotic, thus the activity of some of the editing systems may be limited in non-dividing cells.

However, because of the intrinsic limitations of viral vectors and non-viral vectors, alternative architectures of delivery were being developed, and DNA nanomachines based on programmable nanostructures of DNA are among the emerging engineering solutions. DNA nanomachine delivery systems take advantage of user-designed programmable DNA structures for therapeutic cargo delivery in vivo and release control. Synthetic DNA strands can be made to self-assemble into predefined nanostructures and conform to the local environment, such as pH or temperature changes, to release therapeutic payloads only at the target site of the disease [10]. Key advantages of DNA nanomachines include biodegradability within human metabolic pathways, favourable biocompatibility, and tunable design via chemical modification and controlled self assembly [10]. Nevertheless, DNA nanomachines face substantial translational hurdles, including poor systemic stability in circulating blood, rapid clearance by immune surveillance, and low tissue penetration within dense cardiac parenchyma. Most performance data derive from in vitro assays, and robust in vivo efficacy in animal cardiovascular models is still limited.

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The unique physiological structure of cardiovascular tissue further exacerbates difficulties of delivery process. Compact myocardial intercellular structure and intact endothelial barrier severely hamper the penetration and diffusion of exogenous editing vectors, leading to an efficiency of myocardial transfection with most delivery systems that remains low. Inflammatory microenvironments are also present in damaged cardiovascular tissues, where the presence of these microenvironments can easily promote degradation of vectors and clearance by immune cells, resulting in lower effective concentration of editing agents in the lesion area. These barriers are tissue-specific physiological barriers and one of the most important challenges to overcome that will enable the clinical translation of cardiac somatic gene editing is beyond the scope of conventional vector optimisation.

2.4. Ethical and societal limitations

Widespread clinical adoption of somatic gene editing for modifying disease-associated genetic variants could drive gradual reductions in population level genetic diversity over time. Although somatic editing does not alter germline genomes, which is ethically distinct from germline modification, large scale clinical utilisation of somatic editing for cardiovascular disease may still exert indirect influences on population genetic diversity.

Gene editing therapeutics are likely to carry high production and treatment costs. This creates risks of healthcare disparity, where wealthier populations can access therapies that cure the genetic condition whereas populations that are less well-off are still stuck on long-term medication. These disparities in access could also exacerbate disparities at the social level in healthcare systems and are highly relevant for chronic CVDs, which impact larger populations of people from all social groups. Somatic gene editing raises broad questions regarding the appropriate scope of human genomic intervention. Ethical considerations for somatic editing differ fundamentally from germline editing. Somatic editing modifies only body cells for disease treatment, with no heritable genomic changes, whereas germline editing alters gametes or embryos and transmits modifications to future generations. Since somatic editing does not modify germline material, concerns over heritable genomic alteration are not directly applicable. Nevertheless, the balance between potential clinical health benefits and risks arising from somatic genomic modification still requires careful evaluation for cardiovascular therapeutic applications.

3. Conclusion

Overall, somatic gene editing shows considerable potential as a durable, disease-modifying treatment for selected chronic cardiovascular diseases that currently require long-term medication management, but its clinical application remains constrained by significant engineering, safety and ethical challenges. Somatic gene editing could potentially shift CVD treatments from a continuous management towards a more durable, mechanism-based therapeutic approach. Moreover, according to evidences from preclinical research, including editing disease-associated mutations in vivo, supports the feasibility of somatic gene editing in CVDs and provides a basis for further clinical development. However, the potential therapeutic benefits are limited by high precise editing, as a major safety concern. Emerging approaches such as sCas9-SSAP illustrate progress towards improving precision, but could not sufficiently ensure complete clinical safety. Additionally, efficient and safe delivery remains a major engineering barrier because viral and non-viral systems have limitations in payload capacity, targeting and safety, while emerging DNA nanomachine systems represent a potential but still developing solution. Ethical concerns, including potential

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effects on genetic diversity, unequal access and the wider societal role of gene-editing therapies, have further demonstrated that successful clinical translation requires consideration beyond technical feasibility.

The significance of somatic gene editing therefore lies in its potential to provide a more durable therapeutic strategy for patients whose cardiovascular conditions require prolonged medication management, potentially reducing dependence on continuous treatment; however, its value should currently be viewed as a promising future direction rather than an established replacement for conventional long-term therapy. Although many findings are still in preclinical or early translation stages, and findings from animal models cannot automatically be translated into long-term human clinical outcomes, along with concerns about long-term safety and a limited scope, the future outlook is appreciable. Therefore, further development in the future could be conducted along four directions: enhance editing specificity by improving editing precision and reducing off-target effects, develop safer delivery systems that are specifically targeted, efficient and safe, establish long-term clinical safety to guarantee durability, safety and therapeutic effectiveness, and address ethical and accessibility issues such as ethical governance and healthcare inequality.

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