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Biologics for cardiovascular diseases: from bench to bedside

Xiaochi Sun[1], Xinmeng Wang[1], Ruikun Jia[1], Jie Tang[2], Xinyu Zeng[2], Fulei Zhao[2], Fanlian Zeng[2], Nongyu Huang[2], Jiong Li[2]✉ and Kaijun Cui[1]✉

The rise of biologics, including recombinant proteins, gene therapies, and cell therapies, is reshaping the landscape of modern therapeutics, offering new strategies to address previously "undruggable" targets. Cardiovascular diseases (CVDs), the leading cause of mortality worldwide, remain inadequately managed by traditional therapies, but biologics offer a paradigm shift from symptom control to disease modification. This review provides a comprehensive analysis of biologics in cardiovascular medicine, focusing on five key biological processes: cardiac regeneration, cardiac reverse remodeling, genetic cardiomyopathy correction, vascular function modulation, and lipid metabolism modulation. Advances in cardiac regeneration are highlighted by the transplantation of pluripotent stem cells, direct reprogramming, stimulation of endogenous adult cardiomyocyte proliferation, and noncell strategies, all of which aim to restore cardiac tissue integrity. In reverse cardiac remodeling, therapies targeting key signaling pathways, metabolic processes, and contractility-enhancing agents offer promising new approaches for CVD management. The development of gene therapies targeting genetic cardiomyopathies, including gene replacement, genome editing, and gene silencing, is discussed. For vascular function modulation, therapies targeting angiotensinogen, natriuretic peptide receptor 1, and the gut microbiome have been explored as innovative approaches to regulate vascular tone and hemodynamics. Finally, lipid modulation therapies, including agents targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) and atherogenic lipoproteins, have redefined the management of dyslipidemia and cardiovascular risk. Collectively, these advancements underscore the transformative potential of biologics to provide targeted, personalized, and disease-modifying treatments for CVD. By addressing both the pathophysiological roots and clinical manifestations of CVDs, biologics represent a promising frontier in cardiovascular medicine.

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INTRODUCTION

Biologics have redefined modern therapeutics, shifting the treatment paradigm from symptom management to disease modification. Over the past two decades, biologics have transformed drug development[1] by targeting previously "undruggable" disease pathways. Their growing impact is evidenced by regulatory approvals and market performance. In 2022, the number of biologics approved by the US Food and Drug Administration (FDA) matched that of small-molecule drugs for the first time,[2] indicating a paradigm shift in drug discovery. By 2023, biologics accounted for 7 of the top-selling drugs globally, collectively generating over $90 billion in revenue.[3] While biologics represent a smaller share of total prescriptions owing to their niche indications and cost, their adoption has grown steadily in specialized fields. This growth reflects the increasing demand for therapies that target complex disease mechanisms, such as cancer, autoimmune disorders, and cardiovascular diseases (CVDs).

Despite being the leading cause of mortality worldwide,[4,5] CVDs are still largely managed with small-molecule drugs.[6] While many of these agents, such as RAAS blockers, effectively attenuate adverse general cardiac remodeling and improve survival by targeting specific signaling pathways, significant gaps remain in addressing key disease-driving mechanisms, such as chronic inflammation, fibrosis, and metabolic dysregulation.[7,8] By modulating complex cellular and molecular pathways, biologics have the potential to address these unmet needs, thereby shifting cardiovascular treatment from symptom control to disease modification.

Although biologics for CVD treatment are still in their early stages of development, recent advances have been promising. Some therapies, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors,[9] have already reached the market, whereas others are advancing toward clinical trials.[10] These developments highlight the growing potential for biologics to become a key component of cardiovascular therapeutics.

In this review, we aim to provide a comprehensive perspective on the role of biologics in CVD (Fig. 1), focusing on their ability to modulate five critical biological processes: cardiac regeneration, reverse cardiac remodeling, genetic cardiomyopathies, vascular function modulation, and lipid regulation. By describing the biologics that have been developed in the cardiovascular field over the past 4 years, which have entered the clinical area and are therefore expected to soon reach human application, this review aims to offer insights into how biologics could transform cardiovascular care, ultimately facilitating the successful translation of biologic therapies from the bench to the bedside.

[1]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China and [2]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, and Collaborative Innovation Center for Biotherapy, Chengdu, Sichuan, China
Correspondence: Jiong Li (lijionghh@scu.edu.cn) or Kaijun Cui (cuikaijunscu@scu.edu.cn)
These authors contributed equally: Xiaochi Sun, Xinmeng Wang, Ruikun Jia

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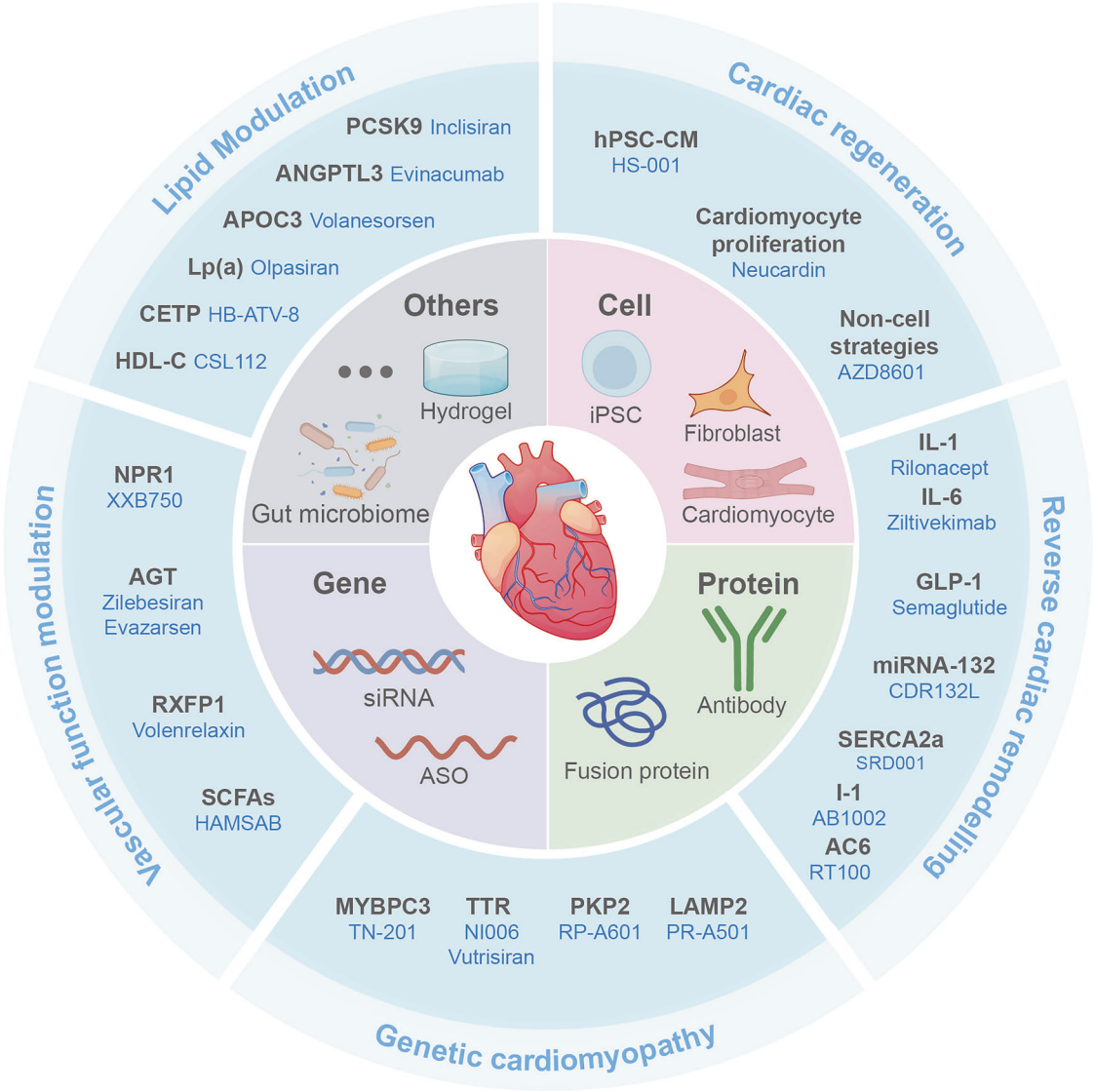

Fig. 1 Biologics for cardiovascular diseases. The biologics commonly used in cardiovascular disease treatment include recombinant proteins, gene therapy, cell therapy, and other biologic products. Functionally, these therapies have made substantial advancements in cardiac regeneration, reverse cardiac remodeling, genetic cardiomyopathy correction, vascular function modulation, and lipid metabolism modulation. The therapeutic targets of these biologics are highlighted in bold black text, while the corresponding representative biologics are listed in smaller blue text. iPSC induced pluripotent stem cell, ASO antisense oligonucleotide, siRNA small interfering RNA, hPSC-CM human pluripotent stem cell-derived cardiomyocyte, IL-1 interleukin-1, IL-6 interleukin-6, GLP-1 glucagon-like peptide-1, SERCA2a Sarcoplasmic/endoplasmic reticulum Ca2+-ATPase 2a, I-1 protein phosphatase inhibitor 1, AC6 adenylyl cyclase 6, MYBPC3 cardiac myosin-binding protein C3, TTR transthyretin, PKP2 Plakophilin 2, LAMP2b lysosomal-associated membrane protein 2b, NPR1 natriuretic peptide receptor 1, AGT angiotensinogen, RXFP1 relaxin/insulin-like family peptide receptor 1, SCFAs short-chain fatty acids, PCSK9 proprotein convertase subtilisin/kexin type 9, ANGPTL3 angiopoietin-like 3, ApoC3 apolipoprotein C3, Lp(a) lipoprotein(a), CETP cholesteryl ester transfer protein, HDL-C high-density lipoprotein-cholesterol (Created with BioRender.com)

OVERVIEW OF BIOLOGICS

Biologics are a class of therapeutic agents derived from biological sources, including proteins, nucleic acids, and living cells. Unlike traditional small-molecule drugs, biologics are typically larger and more complex, offering targeted treatment strategies with high specificity and fewer off-target effects.[1] The diverse nature of biologics allows them to address a wide range of diseases by modulating immune responses, cellular processes, or metabolic pathways.

Biologics can be broadly categorized into three groups: protein therapies, gene therapies, and cell therapies. Protein biologics often function through receptor binding or neutralization of specific targets, whereas gene biologics aim to correct genetic defects or modulate gene expression. Cell therapies offer regenerative potential by replacing damaged tissues or inducing cellular reprogramming. Each category is associated with distinct technological innovations that have expanded their clinical applications.

Protein agents, particularly monoclonal antibodies (mAbs), have become a cornerstone in the treatment of numerous diseases,[11,12] including cancer, autoimmune disorders, and CVDs. Advances in antibody engineering have expanded their utility beyond single-target binding to include bispecific antibodies and engineered proteins with increased binding specificity and pharmacokinetic profiles. Early mAbs targeted a single antigen, but recent advances have led to the development of bispecific antibodies that can

simultaneously target multiple antigens, increasing their therapeutic potential.[13,14] For example, emicizumab is a bispecific antibody that targets both factor IXa and factor X,[15] suggesting a novel approach for treating hemophilia A, a bleeding disorder. This innovation will increase the therapeutic potential of mAbs in CVD, where multiple signaling pathways need to be modulated. In addition, protein engineering technologies have been applied to optimize mAbs,[16,17] aiming to extend their serum half-life and enhance their therapeutic efficacy. Lerodalcib is a novel engineered protein-based biologic designed to reduce serum low-density lipoprotein-cholesterol (LDL-C) by inhibiting PCSK9. Structurally, Lerodalcibep is a fusion protein that binds the interaction domain of PCSK9 with human serum albumin.[18] This design not only increases its binding specificity to PCSK9 but also extends its half-life, allowing for convenient once-monthly subcutaneous injection.

Gene therapies have experienced unprecedented growth, fueled by breakthroughs in RNA therapies, gene-editing technologies, and nonviral gene delivery systems. This progress has been accelerated, particularly by the success of mRNA vaccines for COVID-19. BNT162b2 and mRNA-1273 were the first authorized mRNA vaccines,[19,20] demonstrating the ability of mRNAs to instruct cells to produce viral proteins and induce immune responses. This technological breakthrough has paved the way for mRNA therapeutics beyond vaccines, enabling applications in genetic, metabolic, and cardiovascular diseases. Advances in delivery systems have expanded the scope of RNA therapeutics. Antisense oligonucleotide (ASO) and RNA interference (RNAi) now enable precise gene silencing with high specificity and enhanced stability.[21] Notably, RNAi therapies targeting PCSK9 have shown significant potential for reducing LDL-C levels, suggesting a novel strategy for lipid modulation in CVD patients.[22] Gene-editing technologies, particularly CRISPR-Cas9, have revolutionized the precision with which genetic mutations can be corrected. Unlike RNA-based approaches, CRISPR-Cas9 allows for permanent correction of genetic mutations. This technology is being explored for the treatment of hereditary CVDs. For example, the correction of pathogenic mutations in transthyretin amyloid cardiomyopathy (ATTR-CM), which is a potential one-time treatment with lasting effects, is under investigation.[23]

Cell biologics leverage living cells to regenerate tissues, modulate immune responses, or deliver therapeutic agents. Many advances have been made in this field in recent years, significantly expanding the scope of cell therapies. Chimeric antigen receptor (CAR)-T-cell therapies involve the genetic engineering of T cells to recognize and eliminate cancer cells. This approach has transformed cancer treatment,[24] particularly for hematologic malignancies. Notable examples include tisagenlecleucel and axicabtagene ciloleucel, which have demonstrated high remission rates in patients with leukemia and lymphoma.[25–27] Recent advancements have aimed to extend CAR-T-cell therapy beyond hematologic cancers to solid tumors and noncancerous pathologies.[28] Although current applications of cell therapies in cardiovascular medicine are focused primarily on regenerative approaches, recent breakthroughs highlight exciting new possibilities. Emerging evidence suggests that CAR-T-cell therapies could play a role in targeting fibrosis in CVD patients. For example, a study demonstrated that CAR-T cells targeting fibrosis-related antigens successfully restored cardiac function in a mouse model of hypertensive heart injury.[28] Emerging strategies, such as the use of in vivo mRNA to transiently generate antifibrotic CAR-T cells, offer promising approaches for cardiac repair.[29] Additionally, organoid technology focuses on growing miniature, three-dimensional tissue structures from stem cells that replicate human organs and has become a powerful tool for disease modeling, drug discovery, and precision medicine.[10,30]

Biologics offer several key advantages over small-molecule drugs, driven by their unique structural complexity and ability to engage diverse biological targets. One of the most significant advantages is their high target specificity, which enables precise modulation of disease-driving pathways while minimizing off-target effects.[1] This feature is especially beneficial for CVD, where targeting maladaptive cardiac remodeling or reducing fibrosis requires precise molecular intervention. Biologics can also address previously "undruggable" targets,[31] such as protein–protein interactions, which are often inaccessible to small molecules. Another notable advantage is the potential for long-lasting therapeutic effects. For example, fusion proteins and RNA therapies can achieve extended half-lives or sustained protein production, reducing the dosing frequency and improving patient compliance.[32,33] Finally, biologics support diverse therapeutic mechanisms, including receptor antagonism, RNA silencing, and immune cell reprogramming, offering more versatile and personalized treatment options for CVD patients.

However, biologics face several critical challenges that limit their widespread application in cardiovascular medicine. Owing to their large molecular size and structural complexity, biologics often exhibit poor stability, requiring stringent storage and handling conditions to prevent degradation.[34] Drug delivery is another major hurdle, as the oral bioavailability of most biologics is poor compared with that of small molecules. Additionally, large biologic molecules have limited permeability through cell membranes, necessitating advanced delivery systems such as lipid nanoparticles (LNPs) and viral vectors. Production scalability poses additional constraints,[35] especially for cell therapies such as iPSC therapies, where patient-specific manufacturing increases production time and cost. High production costs further hinder the accessibility of biologics, particularly in resource-limited healthcare systems. In addition, the immunogenicity of biologics is a major challenge affecting drug efficacy and safety. Addressing these limitations is essential for the successful translation of biologics from the bench to the bedside in cardiovascular care.

CARDIAC REGENERATION

Cardiac regeneration remains a major challenge in cardiovascular medicine, as the adult mammalian heart possesses limited regenerative capacity, making the restoration of damaged myocardium largely ineffective. Consequently, biologics-based regenerative strategies have emerged as promising therapeutic avenues for patients with ischemic cardiomyopathy or heart failure (HF). These approaches primarily include pluripotent stem cell transplantation, stimulation of endogenous cardiomyocyte proliferation, direct reprogramming of cardiac fibroblasts into cardiomyocytes, and noncell strategies. In recent years, the ability of human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) to integrate into the host myocardium and generate functional cardiac tissue has been demonstrated,[36] with several clinical trials actively evaluating their efficacy and safety. However, heterologous cell transplantation still faces challenges related to immune rejection, low engraftment rates, and potential tumorigenicity, prompting the exploration of alternative strategies.[37] Stimulating endogenous cardiomyocyte proliferation has been proposed as a more cautious yet promising approach, as direct activation of key signaling pathways has been shown to increase cardiomyocyte proliferation, despite the low basal turnover rate in adult mammalian hearts.[38] Another promising strategy involves direct reprogramming of noncardiomyocytes, such as cardiac fibroblasts, into cardiomyocytes, a process that may facilitate myocardial repair while mitigating fibrosis following ischemic injury.[39] In addition, other promising therapies, including vascular regeneration strategies, extracellular vesicle therapy, and advanced biomaterials, have shown encouraging preclinical potential for patients with myocardial infarction (MI) or advanced HF with reduced ejection fraction (HFrEF) (Fig. 2).

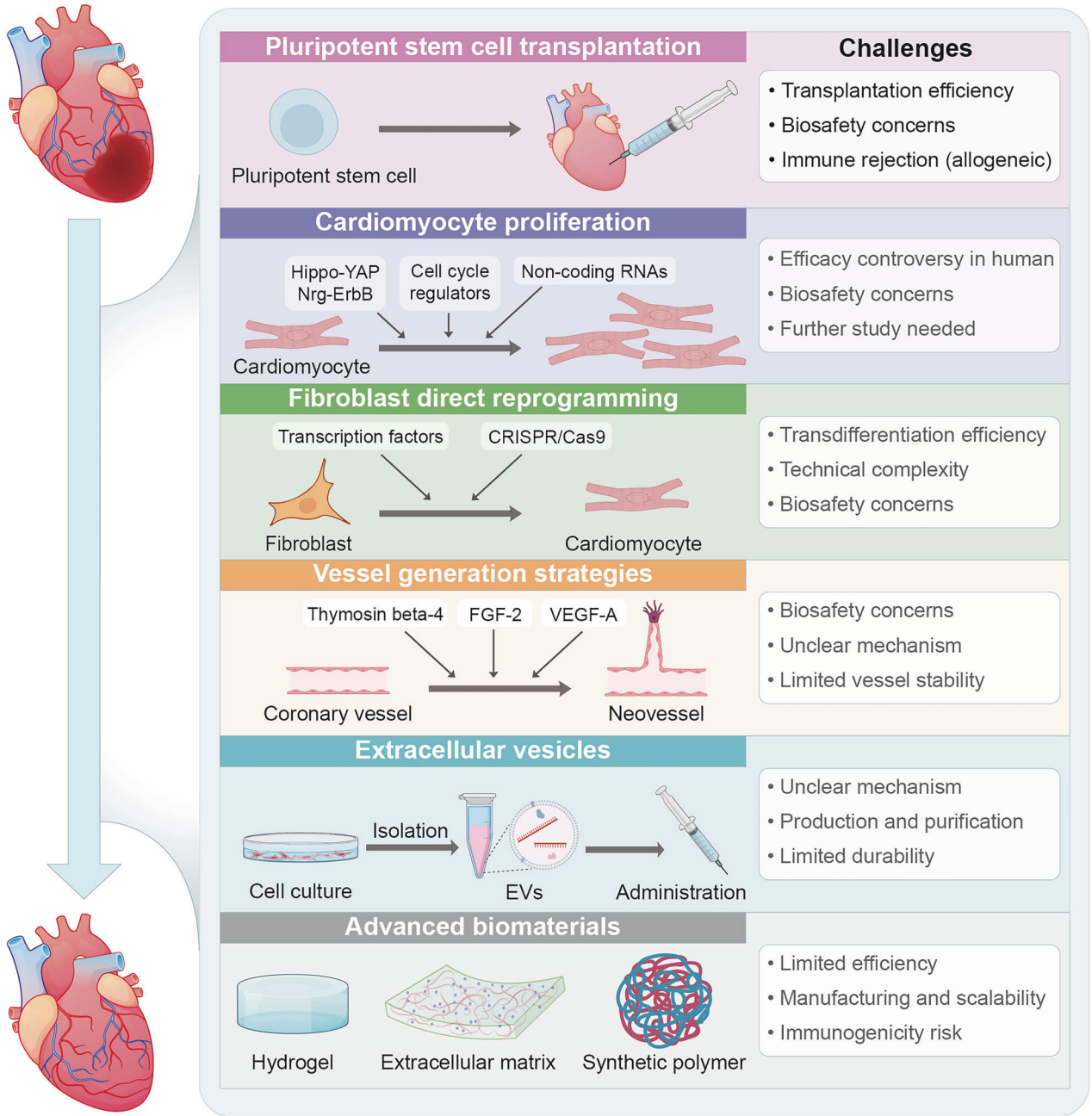

Fig. 2 Current advances in cardiac regeneration strategies. Promising cardiac regenerative therapies include pluripotent stem cell transplantation, direct reprogramming of cultured cardiomyocytes, vessel generation strategies, extracellular vesicles, and advanced biomaterials. Each of these approaches has its own advantages and faces different challenges. YAP Yes-associated protein, Nrg neuregulin, FGF-2 fibroblast growth factor 2, VEGF-A vascular endothelial growth factor A, EVs extracellular vesicles (Created with BioRender.com)

Transplantation of pluripotent stem cells

Recent advancements in the understanding of cardiac regeneration mechanisms have elevated regenerative cardiology to a field of paramount importance, offering the potential to restore cardiac function and improve patient outcomes. The transplantation of pluripotent stem cells represents a leading-edge strategy in cardiac regeneration research. In 2017, a consensus statement on cardiomyocyte regeneration therapy was published, highlighting that the transplantation of cardiomyocytes derived from human pluripotent stem cells (hPSCs) has the potential to generate new myocardial tissue.[40] However, it was concluded that the injection of bone marrow or mesenchymal stromal cells into cardiac tissue does not result in significant transdifferentiation into cardiomyocytes, suggesting that not all 'multipotent' stem cells are capable of differentiating into cardiomyocytes and repairing cardiac tissues.

With the advent of human embryonic stem cells and human induced pluripotent stem cells (hiPSCs), the production of cardiomyocytes with a purity exceeding 90% has become feasible.[41,42] Both hiPSCs and human embryonic stem cells are capable of differentiating into cardiomyocytes and are therefore categorized as hPSCs, which generate hPSC-CMs. The predominant methodologies for the application of hPSCs include the intramyocardial injection of cellular suspensions or spheroids, as

well as the implantation of preconfigured 3D cardiac tissues such as cardiac patches.[43,44] Xenogenic hPSC applications in nonhuman primates and allogeneic transplantation of cynomolgus monkey iPSC-CMs have yielded comparable results under strong immunosuppression.[45] Several studies have demonstrated that hPSC-CM grafts maintain viability over 12 weeks,[46,47] yielding heart muscle in recipient hearts, which is theoretically capable of providing mechanical support for an injured heart. Currently, eight clinical trials are actively recruiting participants with heart failure with a reduced ejection fraction (HFrEF) to evaluate the efficacy and safety of hPSC-CMs transplantation[48,49] (NCT04945018, NCT04396899, NCT05647213, NCT05068674, NCT05566600, NCT03763136, and NCT05223894).

Despite promising prospects, the transplantation of hPSCs to regenerate cardiac muscle still has intrinsic challenges, and ongoing research is directed at overcoming these limitations to increase therapeutic efficacy. The first major challenge is the low transplantation efficiency, with estimates suggesting that only ~10% of transplanted cells persist posttransplantation relative to the initial cell input. This low efficiency is attributed primarily to immediate cell loss through retrograde leakage along the injection tract and cellular dispersal through the cardiac venous and lymphatic vasculature.[50,51] To improve cell retention, the formation of cellular spheroids from iPSCs and transepicardial injection in conjunction with a gelatin hydrogel has demonstrated higher retention rates and enhanced functional restoration in cryoinjured mice and pig hearts.[52] This strategy has been applied in a phase 1/2a clinical trial (NCT04945018) conducted by the Fukuda group and HeartSeed/NovNordisk.[53] Another reason for the low transplantation efficacy is the high rate of cell death. An investigation revealed a notable 17.8% rate of apoptosis among hPSC-CMs within the first 24 h post-injection, even in athymic rats without disease. This may be attributed to several factors, particularly hypoxia and inflammation after MI. A strategy to increase engraftment and transplantation efficiency is to implant hPSC-CMs as three-dimensional structures on the epicardial surface rather than delivering them via intramyocardial injection. Researchers have developed engineered heart muscle allografts composed of induced pluripotent stem cell-derived cardiomyocytes and stromal cells, which have significantly increased engraftment efficiency—both in cryoinjured guinea pig hearts and healthy porcine hearts.[54] On the basis of clear evidence from a clinically relevant homologous large animal model demonstrating sustained and functionally relevant remuscularization without unacceptable adverse effects,[48] this approach has received regulatory approval for a first-in-human phase 1/2 clinical trial (NCT04396899). Recent studies have shown that hPSC-CMs undergo proliferation and clonal expansion following transplantation.[55] Two weeks after transplantation, the average number of new cells from each parent cell was 1.77, and by six weeks, it had increased to 5.41. This discovery offers a conceptual framework for improving the outcomes of transplantation by fostering the proliferation of transplanted hPSC-CMs. Administration of hPSC-CMs with CCND2 overexpression augments cardiomyocyte expansion within both grafts and the infarcted myocardium in mouse and pig models.[56,57] Although direct injection of CCND2-overexpressing hPSC-CMs is not applicable in humans due to safety concerns, this strategy underscores the potential of pro-proliferative interventions to significantly increase the efficacy of hPSC transplantation. For example, coadministration of hPSCs and hydrogels releasing pro-proliferative factors such as Delta-1 has been shown to notably amplify the proliferation of hPSC-CMs post-MI.[58] In addition, enhancing the interaction between hPSC-CMs and other stromal cells can increase cellular viability. This enhancement can be demonstrated either by the injection of hPSCs that transiently express angiogenic proteins or through concomitant administration with endothelial cells.[59,60] Engineered heart muscle (EHM), a tissue-engineered cardiac patch produced by coculturing iPSC-CMs and supportive stromal cells in a 3D bovine collagen type I hydrogel scaffold designed to structurally and functionally mimic native myocardium, has been proven to be effective in rhesus macaques.[48]

The second major constraint associated with hPSC transplantation is safety. Following injection, electrical coupling between hPSC-CMs and the host myocardium can trigger arrhythmogenic events. The differing automaticity of hPSC-CMs compared with native CMs may account for this risk. Although hPSC-CM automaticity decreases with maturation, the occurrence of severe ventricular arrhythmias posttransplantation has hindered its clinical application.[45,47] Notably, iPSC-derived cardiomyocyte transplantation in rhesus macaques sometimes results in unintended osteochondral differentiation, although without apparent detrimental consequences.[48] Gene editing and pretransplant cardiomyocyte processing have been explored to improve differentiation efficacy, inhibit the automaticity of hPSC-CMs, and reduce arrhythmia risk.[61] Recently, a distinct arrhythmogenic cell subset ($SIRPA^+CD90^-CD200^+$) has also emerged as a potentially efficacious therapeutic target for the mitigation of post-transplant arrhythmias.[62] The principal impediment to the clinical application of allogeneic hPSC-CM transplantation is the obligatory utilization of long-term immunosuppressive drugs to avoid allograft rejection. Strategies under investigation include the development of “universal hypoimmunogenic hPSCs,” which trigger a weaker immune response.[63] The use of autologous hiPSCs derived from patients is another promising strategy to reduce the need for immune suppression,[64] and it has been applied in a clinical trial involving children with hypoplastic left heart syndrome (NCT05647213).

Stimulation of endogenous adult cardiomyocyte proliferation

Given the unresolved safety concerns associated with hPSC transplantation, there is a growing consensus that leveraging endogenous cardiac tissue may offer a safer and more practical alternative. Studies have shown that adult mammals, including rodents and humans, exhibit a modest cardiomyocyte turnover rate, estimated at 0.5–2% annually. This low turnover rate is attributed primarily to the limited proliferation of preexisting cardiomyocytes rather than the activity of cardiac stem or progenitor cells.[40] Initially, the regenerative potential of the heart was thought to stem from c-Kit+ progenitor cells residing within cardiac tissue or originating from bone marrow.[65] However, subsequent studies revealed that c-Kit+ cells have a minimal effect on cardiac regeneration.[66]

Directly targeting key signaling pathways involved in cardiac regeneration has been shown to stimulate the proliferation of mature cardiomyocytes. Since Poss’s pioneering work on zebrafish heart regeneration[67] over two decades ago, researchers have identified four major signaling pathways that regulate cardiac regeneration: the Notch, Hippo–YAP, NRG1/ErbB/PI3K/ERK, and β-catenin pathways. Notch-induced cardiac regeneration was first discovered in 2003.[68] However, dual observations that both inhibition and overactivation of Notch can impede cardiac regeneration underscore the intricacies of Notch signaling in this process.[69] The Hippo–YAP pathway is another highly conserved pathway related to the cardiomyocyte cell cycle. Hippo inhibition leads to overactivation of the downstream effector YAP, resulting in increased expression levels of proliferative genes, which reverses cardiac function after MI.[70,71] Neuregulin 1 (NRG1), through its receptors ErbB2 and ErbB4, also plays a pivotal role in cardiomyocyte proliferation and heart regeneration in both mouse and zebrafish models by activating key signaling cascades, such as ERK, Akt and GSK-3β/β-catenin.[72,73]

Given the multifaceted roles of NRG1 in regulating cardiac development, promoting myocardial regeneration, enhancing pump function, and mitigating fibrosis observed in preclinical studies,[74,75] its potential in HF therapy has garnered considerable

attention within the cardiovascular medical community. Clinical trials[76–78] have focused primarily on improving the left ventricular ejection fraction (LVEF), which is attributed to the ability of NRG1 to increase sarcoplasmic reticular calcium reuptake and reduce cardiomyocyte stiffness.[79,80] Neucardin, a recombinant human NRG1β2 protein containing the essential domains for ErbB2/ErbB4 activation, has been shown to significantly improve cardiac function in phase II clinical studies of patients with chronic HF.[77] Neucardin was shown to reduce end-systolic and end-diastolic volumes, which underscores its antiremodeling properties. Two ongoing phase III trials aimed to further validate the effects of Neucardin on cardiac function (CTR20230733) and survival rates (NCT03388593) in patients with chronic HF. If the trials demonstrate efficacy, Neucardin could apply for conditional marketing approval by the China National Medical Products Administration.

In brief, the NRG1/ErbB pathway has demonstrated beneficial effects in various animal models of HF,[74,81] making NRG1-like biologics promising therapeutic strategies. The selective ErbB4 agonist JK07 is currently in phase II clinical trials (NCT06369298). Preliminary data suggest that a single dose of JK07 was safe and efficient, and the mean absolute increase in LVEF on day 180 was as high as 12% (0.09 mg/kg).[82] Research into the application of the Hippo–YAP pathway in CVD treatment is also in the preclinical stage.[83] Gene therapies mediated by adeno-associated virus (AAV) targeting the key negative regulator Sav1 in the Hippo–YAP pathway can promote the nuclear translocation of YAP, thereby activating a series of genes related to cell proliferation and repair and enhancing the regenerative capacity of cardiomyocytes post-MI.[71]

Recent studies have demonstrated that cardiac regeneration is profoundly influenced by noncoding RNA (ncRNA) networks, which have been comprehensively reviewed and summarized from multiple perspectives.[84–87] High-throughput screening and animal model experiments have identified several key ncRNAs involved in CM proliferation. For example, miR-199a has been shown to promote endogenous cardiomyocyte proliferation and enhance cardiac repair.[88–91] A notable study using a porcine model of MI revealed that treatment with adeno-associated virus serotype 6 encoding miR-199a (AAV6-miR-199a) significantly improved overall and regional contractility, increased the myocardial mass, and reduced the scar size.[87] However, the uncontrolled and persistent expression of miR-199a led to sudden cardiac death in most pigs, underscoring the potential risks associated with prolonged miRNA expression. This study reveals the risks associated with ncRNA-based therapies in cardiac regeneration, thereby presenting significant challenges for the clinical translation and broader application of this promising therapeutic approach.

Newborn mammals have the capacity to regenerate substantial myocardium following cardiac injury via cardiomyocyte proliferation; however, this regenerative potential is rapidly lost shortly after birth.[92,93] This decline is attributed to a combination of cell cycle arrest,[94,95] metabolic transitions,[96] and epigenetic regulation.[97] Consequently, reactivating embryonic-like gene expression profiles in adult cardiomyocytes has emerged as a promising strategy to stimulate their proliferation.[98] One approach involves the autoregulated overexpression of key cell cycle regulators,[99,100] including CDK1, CDK4, CCNB1, and CCND1, which have been shown to induce 15–20% proliferation of mature cardiomyocytes and improve post-MI outcomes. Additionally, the deletion of Meis1,[101] a key transcriptional regulator of the cell cycle and its cofactor Hoxb13,[102] has been found to extend the proliferation window of postnatal cardiomyocytes and reactivate mitosis in adult hearts. Upregulating Myc, SOX2, OCT4, and KLF4 in cardiomyocytes prior to and during MI can promote the dedifferentiation of mature cardiomyocytes, thereby reactivating the cell cycle and enhancing myocardial regeneration.[103] Notably, the fetal-like state induced by mimicking embryonic gene expression profiles is typically transient[99] or reversible,[103] minimizing the risk of uncontrolled cell division and cardiac tumor formation. However, the current inability to reliably maintain this transitional state presents a major obstacle to therapeutic advancement.

In brief, stimulation of endogenous adult cardiomyocyte proliferation represents a promising strategy for cardiac regeneration. Key pathways, such as the Notch, Hippo–YAP, NRG1/ErbB, and β-catenin pathways, play pivotal roles in reactivating the cardiomyocyte cell cycle, while ncRNA networks further increase regenerative potential. The development of biologics and gene therapies targeting these pathways, such as AAV6-miR-199a and NRG1-like biologics, has shown considerable potential. Future research should aim to balance regenerative efficacy with safety, exploring methods to only transiently induce gene expression to stimulate cardiomyocyte proliferation or limit proliferation through self-regulating systems.

Direct reprogramming of resident fibroblasts into cardiomyocytes

Direct reprogramming of nonmyocyte cardiac cells into cardiomyocytes has emerged as a promising therapeutic strategy for cardiac repair. Typically, cardiac fibroblasts are activated after MI and are recruited to the injury site to form scar tissue, which replaces damaged myocardium.[98] Reprogramming these fibroblasts into functional cardiomyocytes represents an attractive strategy for cardiac repair following ischemic injury. The potential benefits include the restoration of lost cardiac function, reduction of scar tissue, and targeted repair of the damaged area.[104–106] Over a decade ago, an in vitro study revealed that a combination of specific transcription factors—GATA4, MEF2C and TBX5 (collectively referred to as the GMT cocktail)—could directly reprogram fibroblasts into functional cardiomyocytes, bypassing the conventional iPSC stage.[107] Subsequent in vivo studies employing a more advanced cocktail (GATA4, HAND2, MEF2C, and TBX5, also known as GHMT) successfully induced cardiac fibroblasts to transdifferentiate into cardiomyocytes post-MI, thereby restoring electromechanical function.[108] Further research revealed that additional factors, such as MESP1 and myocardin, are required to reprogram human fibroblasts into cardiomyocytes, highlighting interspecies differences in reprogramming requirements.[109]

Recent investigations have identified additional factors that mediate the transdifferentiation of fibroblasts into cardiomyocytes, including Notch signaling and ZNF281.[110,111] Advances in modern biotechnology have further deepened our understanding of fibroblast reprogramming. For example, single-cell transcriptomics has enabled researchers to map the trajectory of programmatic reorganization and identify new intermediate cell populations.[112] Additionally, the application of CRISPR/Cas9-based transcriptional activation systems has facilitated the reprogramming of human fibroblast lines into cardiac progenitor cells, which can subsequently differentiate into cardiomyocytes, smooth muscle cells, and endothelial cells.[113] However, a critical challenge remains: the low efficiency of reprogramming fibroblasts into cardiomyocytes. Reprogramming efficiency remains low,[107,114] and the survival rate of transplanted cells following in vitro cardiac reprogramming is even lower. For example, in the mouse MI model, fewer than 1% of transplanted cells remain in the mouse heart one week after intramyocardial injection, highlighting the need for strategies to improve reprogramming efficiency.[114] Studies have demonstrated that growth factors, such as transforming growth factor inhibitors and Wnt inhibitors, can increase the efficiency of programmed rearrangement and the in vivo induction of cardiomyocytes.[115] Although successful transdifferentiation of fibroblasts into cardiomyocytes has been achieved in vitro, the reprogramming of human fibroblasts in vivo remains a challenge. The primary challenge lies in maintaining therapeutic concentrations of transdifferentiation-inducing

molecules within the infarct zone, as rapid systemic dispersion leads to suboptimal local bioavailability and potential off-target effects. Prior to clinical implementation, targeted delivery systems must be developed to achieve effective intramyocardial retention of reprogramming factors while maintaining therapeutic safety.

Vessel generation

Revascularization lies at the heart of cardiac repair, and emerging vessel generation strategies offer a multifaceted approach to enhance regeneration beyond singular cell-targeted therapies. In preclinical models, growth factors such as vascular endothelial growth factor A (VEGF-A) and fibroblast growth factor 2 have been shown to have protective effects on myocardial injury by enhancing blood flow restoration.[116,117] Thymosin beta-4, a peptide that promotes epicardial angiogenesis, has been shown to significantly increase the regenerative capacity of cardiomyocytes following MI.[118] Clinical trials of VEGF-A and fibroblast growth factor 2 have shown moderate improvements in myocardial perfusion in patients with coronary artery disease, which may aid in cardiac repair post-MI.[119,120] To improve bioavailability and maximize therapeutic potential, a phase II clinical trial in which naked mRNA encoding VEGF-A was injected into the human heart was conducted.[121] In this randomized, double-blind study, patients who underwent coronary artery bypass grafting received 30 epicardial injections (total 3 mL) of VEGF-A mRNA (called AZD8601) or placebo during surgery. Although the sample size was insufficient to confirm statistical significance, exploratory analysis suggested potential improvements in LVEF, patient symptoms, and brain natriuretic peptide (BNP) levels. These findings support the potential of direct injection of nonlipid-encapsulated naked mRNA for vessel generation as a feasible and safe strategy for cardiac regeneration.[121,122]

Extracellular vesicles

Extracellular vesicles (EVs) are nanoscale vesicles secreted by various cell types that are encapsulated by a lipid bilayer and contain multiple types of bioactive molecules. Through paracrine signaling,[123,124] endogenous EVs mediate intercellular communication and have demonstrated therapeutic potential for cardiac regeneration following acute myocardial infarction (AMI). The therapeutic efficacy of EVs has been validated in multiple large animal models.[125–129] A recent preclinical study demonstrated that both catheter-based coronary delivery and intramyocardial injection of EVs derived from human cardiac progenitor cells significantly increased the LVEF and left ventricular stroke volume in an AMI pig model. Notably, catheter-based coronary delivery was shown to be safer and more effective, aligning better with current clinical practices.[130] The ultimate goal of biomedical research is clinical translation, and the clinical application of EVs in treating cardiac diseases is in its early stages.[130,131] Three clinical trials have been registered to evaluate the therapeutic effects of EVs in patients undergoing percutaneous coronary intervention (NCT04327635), postcoronary artery bypass grafting (NCT05669144), and nonischemic dilated cardiomyopathy (NCT05774509). These trials aim to address key challenges related to the safety and efficacy of EV administration, particularly after intravenous and cardiac injections. Despite their considerable therapeutic potential, the exact mechanisms underlying EV-mediated cardiac regeneration remain incompletely understood, reflecting the intricate interplay between their heterogeneous cargo, recipient cell specificity, and the evolving postischemic tissue microenvironment. To advance clinical translation, future investigations must not only decipher these molecular mechanisms in greater detail but also develop optimized protocols for EV isolation, cargo modification, tissue-specific delivery systems, and large-scale manufacturing to maximize therapeutic efficacy.

Advanced biomaterials

Cardiac tissue engineering aims to restore cardiac function by supporting, substituting, or repairing damaged tissues[132] through the development of hydrogel systems, 3D scaffolds, 3D printing, cardiac patches, and organ-like structures. Hydrogels play a crucial role in cardiac tissue engineering by providing mechanical support and promoting ventricular wall thickening postmyocardial infarction.[133,134] Algisyl-LVR[135] and IK-5001,[136] two hydrogels based on alginate, have progressed to clinical trial stages. Preliminary studies indicate that hydrogels can enhance cardiac regeneration and function without causing safety issues. Additionally, the use of the extracellular matrix as an injectable scaffold for cardiovascular tissue engineering has shown practicality and potential. VentriGel, a hydrogel derived from decellularized porcine extracellular matrix, may promote vascular regeneration and enhance the regenerative capacity of cardiac progenitor cells.[137–139] A phase I clinical trial confirmed the safety and feasibility of intramyocardial injection of VentriGel in patients with impaired left ventricular function post-MI.[140] These promising outcomes will drive the clinical translation of novel biomaterials such as conductive hydrogels,[141,142] triggerable hydrogels,[143,144] and smart stimulus-responsive hydrogels.[145] Moreover, various types of cardiac patches have shown promising therapeutic effects and clinical potential in many in vivo and in vitro studies.[43,146] With advances in material science and further exploration of repair-promoting mechanisms under mechanical support, researchers have designed patches with good mechanical properties, adhesiveness, conductivity, degradability, and vascularization.[43]

Moreover, advanced biomaterials help cardiac regeneration beyond simply providing mechanical support. For example, combining collagen-derived nanogelatin (Gel) with the PI3K inhibitor BEZ-235 greatly enhances the structural and functional maturation of iPSC-CMs.[147] Additionally, by incorporating advanced hydrogel-based delivery systems, the targeted administration of therapeutic agents such as growth factors and small RNAs can be optimized to minimize off-target effects while maximizing cardiac functional recovery.[148]

Limitations and perspectives

PSC-based therapies. While increasing cardiovascular regeneration holds promise for improving outcomes after cardiac injury, significant challenges remain before cardiovascular regeneration can be widely applied. Direct transplantation of hiPSCs and ESCs has recently gained attention as a potential therapy, yet several obstacles hinder its clinical translation. Beyond low transplantation efficiency, safety concerns continue to limit the rapid and deeper advancement of stem cell therapy in cardiovascular regeneration. All patients who undergo allogeneic hPSC (even hypoimmunogenic hPSC) transplantation require continuous immunosuppressant administration, which leads to infection susceptibility and oncogenic risk.

Given these serious iatrogenic consequences, hPSC transplantation currently remains viable only for the treatment of critical, life-threatening conditions where the potential benefits outweigh these substantial risks. Autologous iPSCs seem to present a safer alternative owing to their inherently low immunogenicity. However, the need for patient-specific manufacturing has reduced the scalability of autologous iPSC therapies, which are time-consuming (months per batch), costly, and resource-intensive. In addition, the delayed timeline makes autologous iPSCs impractical for acute conditions such as myocardial infarction.

Ethical concern is another factor limiting hPSC advancement, especially the moral controversy surrounding ESC derivation owing to embryo destruction and the need for rigorous informed consent regarding donor cell usage, commercialization, and genetic privacy. These challenges necessitate stringent regulatory frameworks, public engagement, and alternative technological

solutions to balance therapeutic potential with ethical responsibility.

Noncell therapies. Targeting regeneration- or reprogramming-associated signaling pathways via peptides and gene therapies represents a promising therapeutic strategy. While this approach was pioneered before human pluripotent stem cell (hPSC)-based therapies, its clinical development has progressed more slowly, with fewer clinical trials being initiated to date. This translational gap stems primarily from the complex interplay within cardiac regenerative signaling networks and substantial safety concerns, including uncontrolled cellular proliferation and potential tumorigenic transformation. For example, the NRG1/ErbB signaling pathway has significant oncogenic effects, as it is expressed in different tissues and is frequently activated in multiple cancer types. Although ErbB4-specific agonists may offer a safer alternative than pan-ErbB activation, emerging evidence indicates that ErbB4 itself can function as an oncogene in various malignancies.[149] These findings highlight the pivotal importance of precise control in the transcriptional activation of target genes. Unfortunately, high-resolution regulatory networks related to physiological and pathological processes are currently lacking. Further elucidation of this regulatory network may help to identify targets that specifically stimulate cardiomyocyte regeneration while not influencing other types of cells. Another strategy is to improve delivery techniques to allow temporal and spatial-specific control of gene transcription. This field is rapidly developing, since advanced delivery systems such as nanoparticle-based systems and antibody–drug conjugates (ADCs) have been applied. Nevertheless, these systems face challenges in identifying truly specific surface markers for cardiac cells, as many proposed markers are either not exclusively expressed in cardiomyocytes or are internalized upon cellular stress. This lack of absolute specificity raises concerns about off-target effects, particularly given the potential for unintended gene activation in noncardiac tissues.

Costs and global access. While biologics offer superior regenerative potential, their high costs and scalability challenges hinder their widespread adoption. Although the economic viability and scalability of biologics vary significantly across approaches, they undoubtedly incur substantially higher costs than small molecules do because of their complex manufacturing and stringent safety monitoring. Small-molecule drugs and biologics are estimated to provide comparable quality-adjusted life-year (QALY) gains, but biologics are almost 5 times more expensive and less cost-effective.[150] Future innovations in scalable biologics, such as hybrid approaches, may help bridge this economic gap.

Global access further complicates implementation, as advanced biologic therapies such as stem cell patches demand specialized facilities and cold-chain logistics, limiting adoption in resource-limited settings. Simpler approaches, such as RNA-based therapies, could integrate more readily into existing cardiology workflows. To bridge these gaps, tiered pricing, public–private partnerships, and modular manufacturing models will be essential to balance innovation with affordability, ensuring equitable translation of these groundbreaking therapies.

CARDIAC REVERSE REMODELING

Cardiac remodeling refers to the geometric and functional adaptations of the heart in response to pathological stimuli. While these changes initially help maintain cardiac output, they ultimately lead to myocardial hypertrophy, excitation–contraction coupling dysfunction, inflammatory responses, alterations in cell survival signaling, and mitochondrial impairments, culminating in HF.[151] Cardiac reverse remodeling (CRR) has emerged as a central therapeutic target in cardiovascular disease management. The CRR describes favorable structural and functional modifications that restore the heart to a more physiological state and can be induced by pharmacological interventions, surgical procedures, physiological events, or lifestyle modifications.[152] The CRR encompasses coordinated adaptations across cardiac cell types and extracellular components, implemented through four key therapeutic approaches, each tailored to specific patient subgroups: (1) Supposing inflammatory remodeling—targeting the interleukin-1 (IL-1) and interleukin-6 (IL-6) signaling pathways has become a promising strategy, with IL-1/IL-6 inhibitors demonstrating anti-inflammatory and cardioprotective effects in clinical trials for recurrent pericarditis and atherosclerotic cardiovascular diseases (ASCVDs). (2) Reversing metabolic remodeling—Particularly in diabetes- and obesity-related HF, glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to improve metabolic homeostasis and significantly reduce major adverse cardiovascular events (MACEs). (3) Reducing postischemic remodeling—enhancing angiogenesis and limiting scar formation not only improves cardiac regenerative capacity but also prevents ischemia-induced myocardial dysfunction and mitigates postischemic HF. (4) Reversal of cardiac fibrosis. (5) Increased cardiomyocyte contractility—Restoring cardiac contractility and pumping efficiency is a key target of gene therapy, particularly through SERCA2a and its regulatory proteins, which modulate intracellular Ca^{2+} dynamics to alleviate symptoms in patients with HFrEF and improve long-term outcomes (Fig. 3).

Inflammatory remodeling

Interleukin-1α (IL-1α) functions as an alarmin that is rapidly released following tissue infection or injury, initiating the early immune response.[153] Simultaneously, IL-1α stimulates macrophages and other immune cells to activate the NLRP3 inflammasome, leading to the cleavage of pro-IL-1β into its mature, biologically active form.[154] The release of IL-1β amplifies the inflammatory cascade by promoting cytokine production, particularly by inducing IL-6 expression in monocytes and macrophages, thereby sustaining inflammation.[155] In the cardiovascular system, persistent IL-1–mediated inflammation contributes to vascular remodeling and adverse myocardial remodeling, thereby accelerating disease progression. In the vasculature, IL-1β activates endothelial cells and vascular smooth muscle cells (VSMCs) through the NF-κB and MAPK signaling pathways, increasing the expression of adhesion molecules and chemokines to facilitate leukocyte infiltration and chronic vascular inflammation.[156] Additionally, IL-1β induces phenotypic switching, migration, and proliferation of VSMCs, leading to pathological vascular remodeling.[157] In the myocardium, IL-1 activates IL-1 receptors on cardiomyocytes and cardiac fibroblasts, promoting apoptosis, interstitial fibrosis, and myocardial remodeling. Moreover, IL-1 inhibits L-type calcium channels, impairing cardiomyocyte contractility and exacerbating heart failure progression.[158] Therapeutic inhibition of IL-1 and its downstream signaling pathways has emerged as a promising strategy for attenuating inflammatory remodeling in cardiovascular diseases. Currently, three IL-1 inhibitors—anakinra, rilonacept, and goflikicept—have demonstrated significant clinical potential in cardiovascular therapy.[159] Anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra), competitively inhibits the binding of IL-1α and IL-1β to IL-1 receptors (IL-1Rs), thereby suppressing IL-1-mediated inflammatory signaling. Rilonacept[160] and goflikicept,[161] which act as soluble decoy receptors, bind to IL-1α and IL-1β with high affinity, preventing their interaction with IL-1R and mitigating downstream inflammatory responses. These therapies not only alleviate inflammation but also hold promise for improving the clinical outcomes of patients with atherosclerosis, MI, and HF.

Recurrent pericarditis is recognized as an autoinflammatory condition that is often driven by inappropriate activation of the innate immune system, particularly involving the IL-1 cytokine family.[162] The IRAP (International Registry of Anakinra for

Pericarditis) study confirmed the safety and efficacy of anakinra in treating recurrent pericarditis in a "real-world" population from 14 specialized pericardial disease referral centers. Anakinra treatment reduced the recurrence rate of pericarditis by sixfold, establishing it as a viable therapeutic option.[163] More strikingly, the impact of rilonacept on the treatment paradigm for recurrent pericarditis was further demonstrated in the RHAPSODY (Rilonacept Inhibition of Interleukin-1 alpha and beta for recurrent pericarditis) study, a phase III randomized controlled trial that showed marked clinical efficacy.[164] During the randomized drug withdrawal phase, 74% of patients in the placebo group experienced recurrence of pericarditis, whereas only 7% of patients in the Rilonacept group experienced recurrence. This robust therapeutic effect led to the FDA's approval of rilonacept in 2021 as the first drug for the treatment of recurrent pericarditis.[165] The long-term extension of the RHAPSODY study further demonstrated that the continued use of rilonacept reduced the risk of recurrence without increasing adverse effects.[166] Moreover, the safety and efficacy of goflikicept, a novel IL-1 blocker, are currently being evaluated in a phase II clinical trial (NCT05673902).[167] If successful, goflikicept could further expand the arsenal of IL-1 antagonists available for the treatment of recurrent pericarditis. Collectively, these findings have enriched the range of first-line therapeutic options targeting the IL-1 signaling pathway in recurrent pericarditis.[165,168]

The application of IL-1 inhibitors has expanded beyond classical inflammatory conditions to include CVDs with nontraditional inflammatory components, such as heart failure and myocardial infarction.[169–171] The ongoing VA-ART4 (Interleukin-1 Blockade in Acute Myocardial Infarction to Prevent Heart Failure) clinical trial (NCT05177822) aims to evaluate the extent to which Anakinra can protect patients from HF-related outcomes over a four-year follow-up period. Moreover, the safety and efficacy of goflikicept in STEMI patients are being evaluated in a multicenter phase IIa clinical trial.[161] Preliminary data indicate that goflikicept can significantly reduce the levels of inflammatory markers; however, its impact on major cardiovascular outcomes remains limited.[172] These mixed findings indicate that IL-1-targeted therapies may be effective only in a subset of MI patients, highlighting the need for further research to identify predictive biomarkers or clinical criteria for patient selection.

In the treatment of ASCVD, the validation of the "inflammation hypothesis" has marked a significant milestone. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) demonstrated that anti-inflammatory therapy reduced the incidence of MACEs by 15% in atherosclerosis patients without affecting lipid levels.[173] This breakthrough highlights the importance of targeting inflammation as a therapeutic strategy for ASCVD. Subsequent subgroup analysis revealed that clinical benefits were directly associated with reductions in interleukin-6 (IL-6) and C-reactive protein,[174] making targeting IL-6 a priority in atherosclerosis research. The ASSAIL-MI (ASSessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction) study assessed the efficacy of tocilizumab in patients with STEMI. In this study, patients received a single infusion of tocilizumab within 6 h of the onset of chest pain. Cardiac magnetic resonance imaging performed 3–7 days later revealed a significant increase in the myocardial salvage index, although the infarct size did not significantly change.[175,176] In addition to its short-term myocardial salvage effects, the long-term cardiovascular benefits of IL-6 antagonists have also been evaluated. Ziltive kimab is an IL-6 monoclonal antibody specifically developed for cardiovascular risk reduction. Phase 2 clinical trials have demonstrated its long-term safety and efficacy.[177–179] The ongoing ZEUS trial (NCT05021835) aims to evaluate the potential of zymokimab to reduce MACEs in patients with ASCVD, chronic kidney disease, and inflammation. This trial is expected to be completed in October 2025. These findings suggest that IL-6 blockade may have short-term cardioprotective effects, particularly in the early phase of AMI.

Metabolic remodeling

Cardiac metabolic remodeling, characterized by metabolic inflexibility, lipotoxicity, glucotoxicity, impaired mitochondrial respiration, and insulin resistance, plays a crucial role in the development of obesity- and diabetes-related cardiac dysfunction.[180,181] Therapeutic strategies that target cardiac metabolism, regardless of disease status, have the potential to promote reverse remodeling and improve cardiac function.[182–184] Among these, glucagon-like peptide-1 receptor (GLP-1R) agonists have garnered significant attention as promising metabolic interventions. Over the past decade, clinical trials have demonstrated that GLP-1R agonists significantly reduce major adverse cardiovascular events (MACEs), including myocardial infarction, stroke, and cardiovascular mortality, particularly in patients with type 2 diabetes.[185–188] In the future, GLP-1R agonists may benefit all patients with metabolic cardiovascular risk by slowing the progression of cardiac remodeling, thereby reducing cardiovascular risk.

The GLP-1 receptor, a G protein-coupled receptor, is widely distributed in pancreatic β cells, gastrointestinal smooth muscle cells, and neurons.[189,190] In addition to their glucose-lowering effects, GLP-1R agonists exert direct and indirect cardiovascular protective effects through diverse molecular mechanisms. Upon activation, GLP-1R signals predominantly through the cAMP-protein kinase A pathway and the phosphoinositide 3-kinase (PI3K)-Akt pathway, leading to increased myocardial metabolic efficiency and contractility.[191,192] In vascular endothelial cells, GLP-1R activation stimulates endothelial nitric oxide synthase (eNOS), promoting nitric oxide (NO) production and improving endothelium-dependent vasodilation.[193] Furthermore, GLP-1R activation suppresses oxidative stress and inflammatory responses in vascular smooth muscle cells (VSMCs), contributing to the stabilization of atherosclerotic plaques.[194]

In addition to these direct effects, GLP-1R agonists also contribute to cardiovascular risk reduction through systemic metabolic regulation. By stimulating insulin secretion and suppressing glucagon release, they enhance glucose homeostasis, whereas their central effects on the hypothalamus suppress appetite and promote weight loss.[195] Moreover, GLP-1R activation confers nephroprotection by reducing glomerular hyperfiltration, attenuating albuminuria, and suppressing renal inflammation.[196] Additionally, GLP-1R agonists mitigate hepatic steatosis by modulating lipid metabolism and inhibiting hepatic lipogenesis, thereby contributing to overall cardiometabolic improvement.[197] Collectively, these pleiotropic effects position GLP-1R agonists as promising therapeutic agents for improving cardiovascular outcomes, extending their benefits far beyond glycemic control.[198,199]

Several GLP-1 receptor agonists have received FDA approval for the treatment of type 2 diabetes and obesity, with some being further indicated for cardiovascular protection. For example, on the basis of the results of large randomized controlled trials, dulaglutide,[200–203] liraglutide,[186,204–206] and semaglutide[207–209] have been shown to reduce the risk of MACEs in patients with CVD. Notably, while initially demonstrated in patients with T2DM, recent landmark trials have shown that semaglutide also significantly reduces primary cardiovascular endpoint events (including cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in obese patients without diabetes, substantially expanding their potential cardioprotective applications. Tirzepatide, a novel dual agonist of glucose-dependent insulinotropic polypeptide and GLP-1 receptors,[210] combines the satiety-promoting effects of GLP-1 signaling with the increased energy expenditure induced by glucagon. Recent clinical trials have demonstrated the superior metabolic regulatory capacity of tirzepatide in obese patients, providing greater cardiovascular benefits.[211] A recent randomized controlled trial involving patients with heart failure with preserved ejection fraction and obesity demonstrated that 52 weeks of treatment with tirzepatide not only improved patient health status but also reduced the risk of a

composite endpoint of cardiovascular death or worsening heart failure.[212,213] The ongoing SURPASS-CVOT trial (NCT04255433) and SURPASS-CVOT trial (NCT06779929) aim to evaluate the impact of tirzepatide on cardiovascular outcomes compared with dulaglutide in patients with type 2 diabetes. The trial results are expected to provide robust evidence regarding the cardiovascular benefits of GLP-1 receptor agonists. As research advances, these peptides may become essential components of cardiovascular care for patients with insulin resistance and heart disease.[184,198]

Sodium–glucose cotransporter-2 (SGLT2) inhibitors represent another key target in metabolic regulation. Mechanistically, since SGLT2 is not expressed in cardiomyocytes, SGLT2 inhibitors exert their cardioprotective effects indirectly by targeting noncardiomyocytes, such as by inducing diuresis, modulating neurohormonal activation, and improving metabolism, rather than through direct actions on cardiomyocytes.[214] Clinically, SGLT2 inhibitors have demonstrated significant benefits in patients with HF, regardless of ejection fraction,[215–218] and SGLT2 inhibitors are also safe and effective in AMI patients.[182,219,220] Although SGLT2 inhibitors are not trending toward biologic development, this evidence strongly supports the therapeutic value of reversing metabolic remodeling in CVD patients.

Postischemic remodeling

The pathophysiological progression from MI to HF can be categorized into four distinct but overlapping stages: early acute injury, the inflammatory response, tissue proliferation and repair, and the adverse remodeling phase.[221,222] Ischemic necrosis of myocardial tissue triggers biomechanical changes during cardiac contraction and relaxation, which activate myofibroblasts to produce excessive collagen. This leads to cardiac stiffness and conduction abnormalities. Prolonged compensatory mechanisms in response to regional dysfunction exacerbate the mechanical load on the heart, ultimately inducing myocardial hypertrophy. Together, excessive fibrosis, increased mechanical load, conduction disturbances, and myocardial hypertrophy establish a vicious cycle that drives adverse cardiac remodeling, culminating in HF.[43] For MI patients at risk of future HF, modulating this mechanism through biological therapies could provide a crucial therapeutic advantage.

MicroRNA-132-3p (miR-132), a stress-responsive regulatory RNA upregulated in cardiac tissue, drives adverse remodeling by suppressing FOXO3 and SERCA2A, making it a promising therapeutic target for HF.[223] CDR132L, a locked nucleic acid drug that targets miR-132-3p, has shown potential in reversing postinfarction cardiac remodeling. Multiple preclinical studies have demonstrated that CDR132L can reduce cardiac fibrosis and improve cardiac function.[223–225] A completed phase I clinical trial confirmed its safety and efficacy in patients with ischemic HF,[226] laying the groundwork for subsequent trials. Currently, a phase II trial (NCT05350969) is ongoing to evaluate the potential of CDR132L to prevent or reverse cardiac remodeling in patients with HFrEF following MI. If successful, this therapy could become a novel treatment strategy for mitigating fibrosis and preserving cardiac function in postinfarction patients. In addition to miR-132 inhibition, targeting miR-92a has also been shown to promote revascularization. In a murine myocardial infarction model, miR-92a inhibition improved endothelial cell function and postinfarction recovery by modulating autophagy-related genes in an endothelium-specific manner.[227] MRG-110, an ASO designed to target miR-92a-3p, is currently under investigation for heart failure treatment (NCT03601052). A phase 1 clinical trial involving 49 healthy volunteers demonstrated that systemic infusion of MRG-110 was safe and well-tolerated while effectively suppressing circulating miR-92a levels and function.[228]

Reversal of cardiac fibrosis

Diffuse myocardial fibrosis is characterized by widespread accumulation of collagen fibers and arises in various chronic cardiac remodeling conditions. This pathological process stems from dysregulated fibroblast-mediated collagen turnover, leading to excessive interstitial and perivascular deposition of type I and type III collagen.[229] Unlike attenuating stress-induced cardiac remodeling, reversing existing cardiac fibrosis remains significantly more challenging. Although interventions such as antihypertensive therapy and valve replacement can resolve chronic cardiac injury, they often fail to reverse the myocardial fibrosis process, suggesting that the fibrogenic process may become self-sustaining.[230,231] In addition, effective reversal requires selective collagen removal while preserving physiological scaffolding, necessitating phenotype-specific therapeutic approaches. While targeting extracellular collagen processing through LOX/LOXL inhibition has the potential to attenuate postischemic fibrosis,[232] clinical trials of LOXL2-blocking simtuzumab have proven ineffective due to enzymatic redundancy.[233] Moreover, currently, no therapeutic option has been approved that directly reverses cardiac fibrosis. Further research into the temporal dynamics of fibrotic remodeling and the development of biomarkers to guide targeted interventions could pave the way for transformative antifibrotic therapies for heart failure.

Enhanced contractility

Contractility is a fundamental characteristic of cardiomyocytes, as it directly determines the ability of the heart to pump blood. Cardiac contractility not only affects symptomatic presentation in HF patients but is also closely associated with long-term prognosis.[234–236] As a result, the development of therapeutics aimed at enhancing cardiac contractility has become a key objective in HF treatment. Sarcoplasmic/endoplasmic reticulum Ca2 + -ATPase 2a (SERCA2a), a pivotal protein in the excitation–contraction coupling process, maintains calcium homeostasis in cardiomyocytes by transporting Ca2+ from the cytoplasm back into the sarcoplasmic reticulum. This function ensures normal cardiac relaxation and contraction. Extensive clinical investigations[237,238] and genetic studies[239] have demonstrated that a reduction in SERCA2a expression or activity is a hallmark of HF, contributing to impaired cardiac contractility and an increased risk of arrhythmias.[239] Studies in various animal models[240–242] have provided strong evidence that enhancing or restoring SERCA2a activity improves cardiac function and prevents HF progression, making it a prime target for clinical translation.

The CUPID (Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) trial was the first gene therapy clinical study targeting SERCA2a in HF.[243] This study aimed to improve myocardial contractility by delivering the SERCA2a gene via an AAV1 vector. Although the phase I results were promising, with some patients demonstrating improvements in left ventricular structure and function, the subsequent CUPID2 trial revealed that AAV1/SERCA2a therapy failed to reduce HF recurrence or delay terminal events.[244] Following the neutral results of CUPID2, patient recruitment for related trials, such as AGENT-HF[245] (NCT01966887) and SERCA-LVAD (NCT00534703), was prematurely halted. This outcome has been attributed to the low transduction efficiency of AAV1 vectors in human cardiomyocytes, highlighting the need for improved gene delivery strategies.[246] To address this issue, ongoing trials such as MUSIC-HFrEF (NCT04703842) and MUSIC-HFpEF (NCT06061549) are exploring the use of patented titration techniques to optimize dosage, aiming to achieve therapeutic efficacy while minimizing adverse effects. Innovative tissue-specific recombinant AAV (rAAV) vectors are also being developed to increase the precision of gene delivery. Strategies such as the construction of chimeric capsids, peptide library screening, and chemical conjugation have been used to improve AAV vector specificity and transduction efficiency.[247] For example, AAV2i8, a chimeric vector of AAV2/AAV8, has demonstrated superior cardiomyocyte transduction capabilities.[248] The gene therapy agent AB1002, which uses the

AAV2i8 vector to deliver the protein phosphatase inhibitor 1 gene, inhibits protein phosphatase 1 activity, thereby increasing the phosphorylation of phospholamban (PLN) and enhancing SERCA2a activity. Preliminary human trial results revealed improvements in the NYHA classification and LVEF after 12 months of treatment with a low-dose coronary infusion of AB1002.[249]

Adenylyl cyclase 6 (AC6) represents another promising target for HF gene therapy, as it enhances myocardial contractility by promoting PLN phosphorylation.[250] A multicenter, randomized, double-blind, placebo-controlled phase II study validated that RT100, an AdV5-encoded AC6 gene therapy, safely increased left ventricular function beyond standard HF treatments.[251] Although the phase III FLOURISH trial of RT100 was originally planned for 2019, it was withdrawn because of business adjustments.[252] Recently, the company announced plans to initiate a pivotal phase 2b/3 trial for RT100, with a formal study plan to be submitted to the FDA.

Enhancing myocardial contractility remains a vital strategy for addressing HF, with gene therapy approaches targeting SERCA2a and AC6 leading the field. While early trials such as CUPID2 yielded neutral results, recent efforts to improve gene delivery vectors, such as AAV2i8, and optimize dosing regimens through patented titration techniques have shown promise. Emerging therapies such as AB1002 and RT100 aim to overcome past limitations and offer innovative approaches to modulating calcium cycling and cardiac contractility. These advances underscore the potential of gene-based interventions to transform the management of HF, offering hope for durable improvements in cardiac function.

Limitations and perspectives

Therapeutic approaches targeting cardiac remodeling reversal, including monoclonal antibodies, peptide-based therapies, and AAV vectors, share similar translational challenges with cardiac regeneration strategies, particularly with respect to delivery efficiency and potential off-target effects. However, interventions targeting cardiac remodeling reversal have demonstrated less favorable efficacy results than cardiac regeneration therapies have, with a higher proportion of negative or mixed primary endpoints in clinical trials. This may be because cardiac regeneration therapies directly restore damaged myocardium, whereas remodeling-focused interventions primarily modulate upstream pathological drivers (e.g., inflammatory cascades or metabolic dysregulation) that operate through complex, interconnected signaling networks to induce structural changes. Moreover, single-pathway interventions often require higher therapeutic doses, increasing the risk of adverse effects. For example, anti-inflammatory therapies may increase infection susceptibility,[173] whereas GLP-1 receptor agonists can induce cardiac muscle loss.[253] These limitations stem from the pleiotropic nature of upstream signaling pathways and their network-level crosstalk, which diminishes the efficacy of monotherapeutic approaches targeting cardiac remodeling.

While therapeutic strategies aimed at enhancing cardiac contractility through the upregulation of SERCA2a or AC6 expression show promise for ameliorating HF symptoms, this approach faces significant limitations. In failing cardiomyocytes, the pathological phenotype includes multiple dysfunctional pathways, extending far beyond the deficiency of proteins related to contraction. Isolated SERCA2a-overexpressing cells may fail to address these broader cellular alterations and could be detrimental. Of particular concern is the risk that increased energetic demands from increased contractility might paradoxically accelerate pathological remodeling processes in already compromised cardiomyocytes, worsening long-term prognosis.

Future therapeutic strategies for reversing cardiac remodeling will likely require combinatorial approaches that target multiple pathological pathways simultaneously and personalized treatment regimens on the basis of individual patient profiles. The successful implementation of such strategies will depend on the development of precisely targeted delivery systems capable of spatial and temporal control of therapeutic agents.

GENETIC CARDIOMYOPATHY CORRECTION

Unlike common cardiovascular diseases such as hypertension and coronary artery disease, which are influenced by multifactorial genetic and environmental factors, several genetic cardiomyopathies are driven primarily by single-gene mutations. This distinction enables precise therapeutic targeting of the molecular drivers underlying disease pathogenesis, making gene therapy a particularly promising strategy. Among the diverse forms of genetic cardiomyopathy, ATTR-CM, hypertrophic cardiomyopathy (HCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) have garnered significant attention because of their high prevalence, well-defined genetic basis, and feasibility of gene-targeted therapies.[254] These conditions share well-characterized pathogenic mechanisms—including protein misfolding (ATTR-CM),[255] sarcomere dysfunction (HCM),[256] and intercellular adhesion instability (ARVC)—which provide clear molecular targets for therapeutic intervention.

Gene therapy strategies can be broadly categorized into three major approaches: gene replacement, genome editing, and gene silencing.[257] Gene replacement refers to the introduction of an exogenous gene to restore functional protein levels in conditions caused by haploinsufficiency or loss-of-function mutations. Genome editing has garnered increasing attention with the advent of CRISPR-Cas9 nucleases, which are adapted from the bacterial immune system and offer the potential for precise correction of pathogenic mutations. This strategy remains in preclinical development for many cardiac disorders but holds promise for addressing the genetic basis of cardiomyopathies. Gene silencing aims to reduce the expression of mutant alleles via the use of ASOs or siRNAs. Given that ARVC and HCM are caused primarily by loss-of-function mutations,[258,259] AAV-mediated gene supplementation has emerged as the predominant therapeutic strategy. In contrast, ATTR-CM, which arises from gain-of-function mutations,[260] has been the focus of all three therapeutic approaches, with multiple candidates already in clinical development (Fig. 4).

Transthyretin amyloid cardiomyopathy

ATTR-CM is a progressive and life-threatening disease characterized by the aggregation of misfolded transthyretin (TTR) into insoluble amyloid fibrils within the heart.[255] TTR, a circulatory protein primarily synthesized in the liver, is responsible for transporting thyroid hormones and retinol and normally exists as a tetramer. However, TTR gene mutations or age-related modifications can destabilize the tetramer, causing it to dissociate into misfolded amyloidogenic monomers that subsequently aggregate into amyloid fibrils.[261] In addition to tetramer dissociation, a recent study using the Ser52Pro TTR variant identified a distinct amyloidogenesis pathway, wherein proteolytic cleavage of native TTR also contributes to amyloid formation in vivo.[262] The accumulation of amyloid fibrils in the cardiac extracellular matrix induces myocardial stiffness and conduction disturbances, leading to clinical manifestations such as HF and arrhythmias.[263] With advances in cardiac imaging and heightened clinical awareness, ATTR-CM is now increasingly recognized as a distinct cause of HF.[264,265] Moreover, the extent of cardiac involvement is a major determinant of ATTR outcomes;[266] thus, the treatment of ATTR-CM has become a focal point of current research. Disease-modifying therapies for ATTR-CM can be classified into three main strategies:[255] (1) stabilizing TTR tetramers to inhibit dissociation, (2) suppressing hepatic TTR synthesis, and (3) promoting the clearance of amyloid deposits via antibody-driven phagocytosis

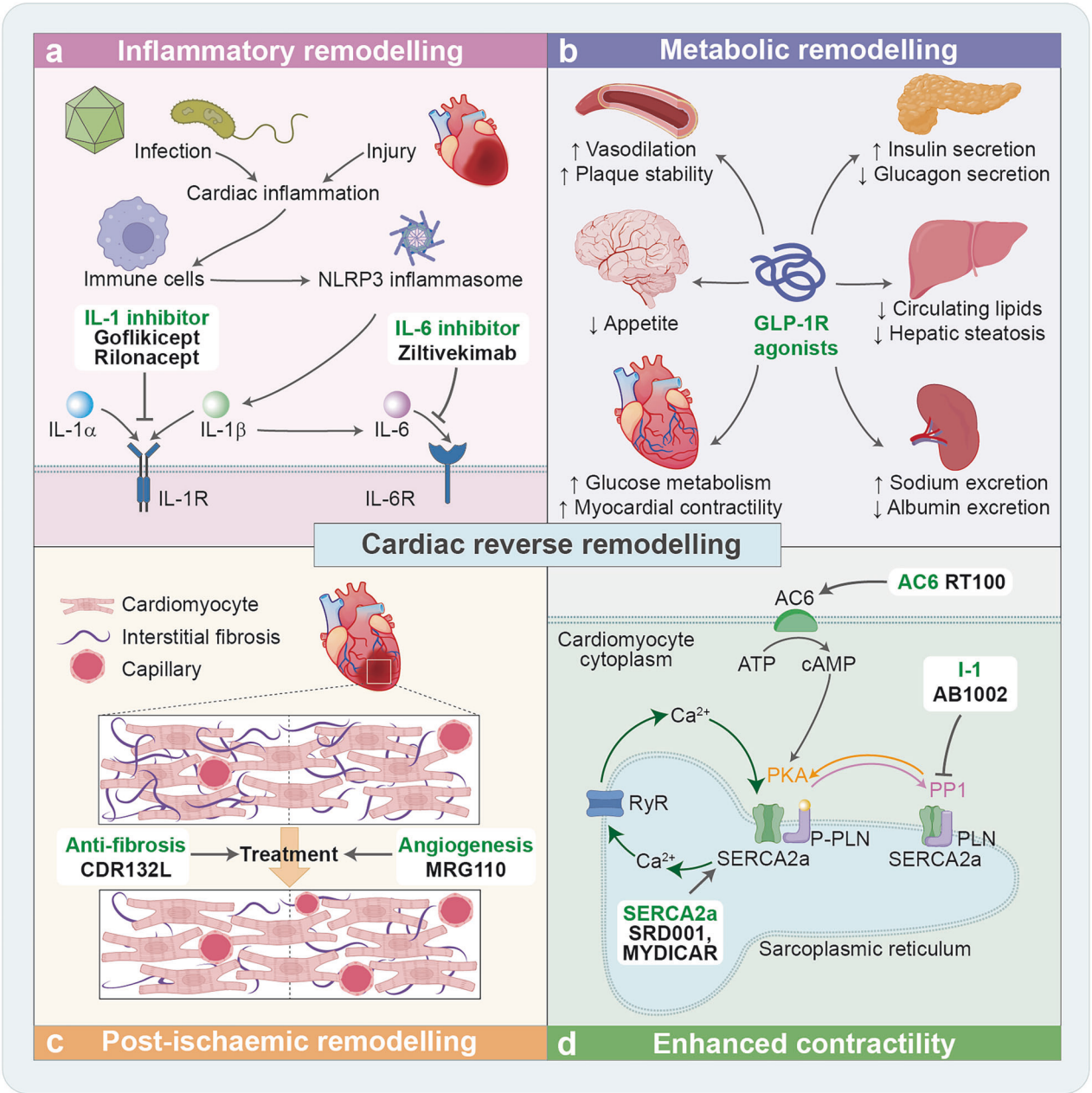

Fig. 3 Therapeutic approaches for reversing cardiac remodeling. **a** Following tissue infection or injury, IL-1α is rapidly released as an alarmin signal, initiating the early immune response. Simultaneously, it stimulates macrophages and other immune cells to activate the NLRP3 inflammasome, leading to the maturation and secretion of IL-1β, which in turn amplifies the inflammatory cascade. IL-1β further induces IL-6 production in immune cells, sustaining the inflammatory response. IL-1 and IL-6 inhibitors mitigate pathological remodeling by competitively blocking cytokine–receptor interactions, thereby suppressing downstream inflammatory signaling. **b** GLP-1R agonists exert direct cardioprotective effects by improving myocardial metabolism and contractility, enhancing vasodilation, and stabilizing atherosclerotic plaques. Additionally, they may contribute to cardiovascular risk reduction through indirect mechanisms, including increased insulin secretion, appetite suppression, renal protection, and the mitigation of hepatic steatosis. **c** Postischemic cardiac remodeling is characterized by excessive myocardial interstitial fibrosis and reduced capillary density. Treatment with CDR132L reduces pathological collagen deposition and fibroblast activation, whereas MRG-110 enhances capillary density by stimulating endothelial cell proliferation and migration. Both therapeutic strategies contribute to reversing postischemic remodeling, ultimately improving cardiac function. **d** SERCA2a is a key regulator of the intracellular Ca^{2+} cycle in cardiomyocytes. Its activity is modulated by PLN, a reversible inhibitor that suppresses SERCA2a function in its unphosphorylated state. PLN phosphorylation, which alleviates its inhibitory effect on SERCA2a, is mediated by PKA downstream of AC6-generated cAMP. Conversely, PLN dephosphorylation is catalyzed by PP1, whose activity is negatively regulated by I-1. IL-1 interleukin-1, IL-6 interleukin-6, IL-1R interleukin-1 receptor, IL-6R interleukin-6 receptor, GLP-1R glucagon-like peptide-1 receptor, SERCA2a Sarcoplasmic/endoplasmic reticulum Ca2 + -ATPase 2a, PLN phospholamban, PP1 protein phosphatase 1, I-1 protein phosphatase inhibitor 1, PKA protein kinase A, AC6 Adenylyl cyclase 6, RyR ryanodine receptor (Created with BioRender.com)

(Fig. 4). Currently, the only FDA-approved therapy for ATTR-CM is tafamidis, a small-molecule TTR stabilizer. However, tafamidis has limited efficacy in preventing declines in quality of life and functional capacity.[267–269] The remaining two therapeutic strategies are still under clinical investigation, with the aim of filling this treatment gap and potentially reversing cardiac dysfunction.

mAbs such as PRX004 and NI301A offer a promising strategy for ATTR-CM treatment by selectively binding to both wild-type and mutant TTR amyloid fibrils, thereby promoting the clearance of existing amyloid deposits. This approach does not interfere with the normal function of physiological TTR tetramers, providing the dual advantage of maintaining normal protein function while reducing the amyloid burden in organs.[270] PRX004, a mAb developed via a structure-based approach,[271] specifically targets epitopes exposed only in monomeric and nonnative conformations of TTR. The phase 1 study in hereditary ATTR patients was prematurely terminated due to the COVID-19 pandemic, but preliminary data revealed that PRX004 was safe and alleviated disease progression in all seven assessable patients.[270] A phase 2 study (NCT05442047) is currently underway to evaluate its efficacy in ATTR-CM patients, with endpoints including the 6-minute walk test and BNP levels. NI301A, another monoclonal antibody, was developed via high-throughput screening of memory B cells from healthy elderly individuals. NI301A has a high binding affinity for disease-associated ATTR aggregates and does not interfere with native TTR tetramers.[272] In phase 1 clinical trials,[273] NI301A demonstrated the ability to reduce cardiac ATTR deposits. Recently, researchers developed a translational pharmacokinetic and pharmacodynamic model by integrating in vitro and in vivo data in a mechanistic and quantitative manner, which revealed a dose-dependent reduction in the cardiac amyloid burden—occurring within 4 months at 60 mg/kg and within 10 months at 10 mg/kg.[274] A subsequent phase III clinical trial (NCT06183931) will assess its efficacy on the basis of all-cause mortality and cardiovascular events. In summary, antiamyloid mAbs have an irreplaceable advantage in clearing existing deposits and are a synergistic and complementary approach to current treatments for ATTR-CM.[275]

Gene silencing via small interfering RNA (siRNA) and ASO technologies offers an effective approach to reduce hepatic TTR production.[276] Patisiran, an FDA-approved siRNA for treating hereditary ATTR polyneuropathy (ATTR-PN), reduces hepatic TTR synthesis and circulating TTR levels.[277] It utilizes an LNP delivery system to efficiently transport siRNA to liver cells, inhibiting the production of both mutant and wild-type TTR proteins. In the APOLLO-B trial (NCT03997383), which enrolled 360 patients with ATTR-CM, compared with placebo, patisiran treatment improved the 6-minute walk distance by 14.7 meters.[278] However, current evidence has not fully established its clinical significance for ATTR-CM, leading to the FDA's rejection of a new supplemental drug for this purpose. Vutrisiran, a second-generation siRNA, employs a more stable N-acetylgalactosamine (GalNAc)-conjugated delivery system, allowing for less frequent dosing.[279] The phase 3 HELIOS-B trial (NCT04153149), a multicenter, double-blind, randomized controlled trial, recently reported that vutrisiran reduced the primary endpoint, a composite of all-cause mortality and recurrent cardiovascular events, by 28% in the overall population and by 33% in the monotherapy subgroup.[280] Importantly, the HELIOS-B trial included patients diagnosed at earlier stages of ATTR-CM with milder clinical manifestations,[264] reflecting a shift toward earlier intervention in ATTR-CM management. Collectively, these data suggest that Vutrisiran may become a new standard of care for ATTR-CM.

Inotersen is an ASO drug that selectively binds to the 3′ untranslated region of TTR mRNA, promoting its degradation and thereby inhibiting the synthesis of both mutant and wild-type TTR proteins.[281] As approved by the FDA in 2018 for the treatment of ATTR-PN, Inotersen requires regular safety monitoring for potential adverse events, particularly thrombocytopenia and glomerulonephritis.[282] Clinical exploration of Inotersen in ATTR-CM is still in progress, with a phase 2 trial (NCT03702829) underway. Eplontersen, a second-generation ASO, employs a GalNAc-conjugated delivery system for enhanced liver targeting, increased safety,[283] and decreased dosing frequency.[284] In a phase 3 clinical trial,[284] eplontersen significantly reduced circulating TTR levels, mitigated nerve damage, and improved quality of life in ATTR-PN patients, resulting in its FDA approval in December 2023 for treating ATTR-PN.[285] Further exploratory analysis revealed that, after 65 weeks of treatment, patients in the cardiomyopathy subgroup experienced improvements in LVEF and left ventricular end-diastolic volume.[286] These findings support ongoing investigations of eplontersen in ATTR-CM (NCT04136171), with a focus on its potential to improve cardiac structure and function.

As a monogenic disease, ATTR amyloidosis represents an ideal target for in vivo gene editing mediated by CRISPR-Cas9. The limited and well-defined function of TTR,[287] combined with the fact that more than 99% of circulating TTR is produced by the liver, provides a clear rationale for therapeutic gene knockout.[288] NTLA-2001, a CRISPR-Cas9-based gene-editing therapy, is delivered via an LNP system for efficient liver targeting.[23] A phase 1 trial of NTLA-2001 demonstrated dose-dependent reductions in serum TTR, with reductions of 52% and 87% at low and high doses, respectively. Importantly, no serious adverse events were reported, highlighting the safety profile of this approach.[289] A phase 3 trial (NCT06128629) is currently underway, enrolling 765 patients with ATTR-CM to evaluate the long-term efficacy and safety of NTLA-2001.

Arrhythmogenic right ventricular cardiomyopathy

ARVC is a progressive cardiomyopathy caused by specific mutations, characterized by the loss of myocardial cells and their replacement with fibro-fatty tissue.[290] This disease typically presents as ventricular arrhythmias and HF and is a major cause of sudden death among young adults.[291,292] Current treatment strategies are limited to symptom relief and lack proven efficacy in modifying the disease course, thus necessitating the development of etiology-based gene therapies. In ARVC clinical cohorts, mutations in the Plakophilin 2 (PKP2) gene are most commonly detected,[293,294] making it a focal point for translational research. Mutations in the PKP2 gene lead to reduced levels of PKP2 protein in the myocardium, impairing the assembly of desmosomes, which are crucial for providing structural stability and facilitating intercellular communication.[295,296] A substantial body of preclinical evidence has demonstrated that AAV-mediated PKP2 gene replacement can improve the molecular and functional aspects of ARVC,[297–300] laying the groundwork for subsequent human studies.

Currently, three AAV-mediated PKP2-related ARVC gene therapies have received FDA approval to enter phase I clinical trials:[301] TN-401 (NCT06228924), LX2020 (NCT06109181), and RP-A601 (NCT05885412). The first two gene therapies utilize the rAAV9 and rAAVrh10 vectors, respectively, to deliver the human PKP2 gene. RP-A601,[297] to enhance cardiac targeting, uses an rAAVrh.74 vector that preferentially binds to striated muscle and is controlled by a cardiac-specific cTnT promoter to express the human PKP2 transcript variant A. Moreover, gene therapies targeting other classic mutations in ARVC,[302,303] such as PLN and desmoglein 2, have also shown promising progress in preclinical studies. While the actual clinical application of gene therapies still faces challenges[304] such as potential toxicity, immunogenicity, and delivery efficiency, the approval of these biologics for clinical trials highlights the growing recognition and validation of AAV-mediated gene therapy as a promising and innovative treatment approach.

Hypertrophic cardiomyopathy

HCM is the most common inherited cardiac disorder, affecting approximately 1 in 500 individuals worldwide.[305] HCM exhibits

marked clinical and phenotypic heterogeneity, often requiring cardiac imaging and histopathological evaluation for diagnosis.[306] Numerous autosomal dominant pathogenic mutations have been identified in HCM, with genes encoding sarcomeric proteins constituting the largest subgroup, accounting for 30–40% of HCM cases.[307,308] Among the known pathogenic genes associated with HCM, mutations in MYBPC3 (myosin-binding protein C3) are the most prevalent,[309] with the majority being loss-of-function variants that result in haploinsufficiency.[309,310] MYBPC3 plays a crucial role in sarcomere organization and contractile regulation by modulating myosin–actin interactions and coordinating titin-based passive tension, thereby ensuring proper sarcomere function and cardiac contractility. Given the essential role of MYBPC3 in sarcomeric integrity, gene replacement therapy represents a direct and promising strategy to restore cardiac function. TN201, an AAV9-mediated gene therapy, aims to restore MYBPC3 protein expression by delivering a functional MYBPC3 gene. This therapy is currently being used in adult patients in a phase 1b clinical trial (NCT05836259), with plans to expand its application to infants with homozygous MYBPC3 mutations in subsequent studies.[311]

Another gene replacement therapy relevant to HCM is RP-A501, which employs AAV9 to deliver a functional copy of the human lysosome-associated membrane protein 2B (LAMP2B) gene. Danon disease is a severe and penetrant genetic cardiomyopathy that affects 1–4% of patients with HCM and is caused by loss-of-function mutations in the LAMP2 gene.[311,312] LAMP2B plays a crucial role in autophagosome–lysosome fusion, a key process in the autophagy–lysosomal pathway essential for cellular homeostasis.[313] Loss-of-function mutations in LAMP2B disrupt lysosomal degradation, leading to the accumulation of autophagic vacuoles, mitochondrial dysfunction, and impaired cellular clearance, ultimately resulting in cardiomyocyte hypertrophy and contractile dysfunction. Clinically, Danon disease manifests as cardiomyopathy, skeletal myopathy, and cognitive impairment, with cardiac involvement being the predominant and most life-threatening feature.[314] Preliminary data from preclinical models[315] and a phase I clinical trial[316,317] have indicated that RP-A501 treatment increases cardiac LAMP2B expression, leading to significant histological improvements in cardiac tissue. A phase 2 clinical trial (NCT06092034) is currently underway to evaluate the safety and efficacy of RP-A501 in male participants aged 8 years and older.

Recent preclinical studies have demonstrated the potential of CRISPR-Cas9 genome editing to address key mutations underlying HCM, such as missense mutations in the MYH7 gene[318,319] and premature stop codon mutations in the MYBPC3 gene.[320] These studies have laid a solid foundation for the clinical translation of CRISPR-based therapeutics in HCM. For example, CRISPR/Cas9 has been shown to repair MYBPC3 truncating mutations, restoring normal protein function in preclinical models. Importantly, the precise, heritable, and permanent nature of CRISPR-Cas9 editing allows for one-time curative interventions, which hold transformative potential for inherited cardiomyopathy. As this technology continues to evolve, efforts are underway to optimize delivery systems and enhance target specificity to minimize the risk of off-target effects. Advances in cardiac-specific delivery vectors and high-fidelity Cas9 variants are expected to accelerate the clinical translation of this approach. Notably, direct gene editing via CRISPR-Cas9 introduces permanent double-strand breaks, which carry risks such as off-target mutations and unintended genomic rearrangements. The application of epigenetic editing, which employs a catalytically dead Cas9 (dCas9) fused to DNA or histone modifiers, offers a safer alternative by modulating gene expression without altering the underlying DNA sequence.[321] For HCM, epigenetic editing can selectively silence mutant alleles while sparing wild-type copies or activate compensatory pathways without permanent genetic changes. However, while epigenetic editing has significant therapeutic potential for hypertrophic cardiomyopathy (HCM), this approach has not yet been experimentally validated in HCM models.

Limitations and perspectives

Biologics have demonstrated more favorable clinical outcomes in patients with genetic cardiomyopathy, likely because of the condition's more singular etiology. In addition to delivery limitations, safety risks, and durability concerns, the small patient populations characteristic of rare diseases pose an additional obstacle. This scarcity hinders robust clinical validation and reduces commercial viability, discouraging sustained investment and broader therapeutic advancement. Adaptive trial designs and international registries may accelerate approvals for these rare diseases. Moreover, recent studies suggest that ATTR-CM is significantly more prevalent than previously recognized.[322] This growing understanding of its epidemiology may incentivize companies to accelerate related therapeutic development efforts.

VASCULAR FUNCTION MODULATION

The regulation of vascular function plays a central role in maintaining blood pressure homeostasis, modulating hemodynamics, and ensuring adequate organ perfusion. This dynamic process relies on the coordinated interplay between endothelial cells and vascular smooth muscle cells (VSMCs), which is influenced by neurohumoral factors, locally acting vasoactive mediators, and metabolic signals.[323,324] In cardiovascular diseases such as hypertension and HF, vascular dysfunction contributes not only to abnormal blood pressure regulation but also to increased cardiac afterload, impaired tissue perfusion, and progressive end-organ damage. Consequently, targeting vascular dysregulation has emerged as a pivotal therapeutic strategy, particularly in blood pressure control and hemodynamic optimization for HF management.

The balance between vasodilation and vasoconstriction is predominantly governed by two key mechanisms:[325] nitric oxide (NO) bioavailability and intracellular Ca^{2+} dynamics within VSMCs. NO, synthesized and released by endothelial cells, activates soluble guanylyl cyclase, leading to cyclic guanosine monophosphate (cGMP) production and a subsequent reduction in the intracellular Ca^{2+} level in VSMCs. This process attenuates actin–myosin interactions, thereby promoting vasodilation. Conversely, an increase in Ca^{2+} levels enhances vascular contractility, elevating peripheral resistance and imposing greater hemodynamic stress on the heart. Many biologic-based therapeutics leverage these pathways, either by enhancing NO signaling and cGMP-mediated vasodilation or by attenuating Ca^{2+}-dependent vasoconstriction, thereby exerting antihypertensive and cardioprotective effects.

Building upon these mechanisms, several biologic-based approaches have been developed to target key regulators of vascular function, including angiotensinogen (AGT), natriuretic peptide receptor 1 (NPR1), relaxin/insulin-like family peptide receptor 1 (RXFP1), and gut microbiome-derived short-chain fatty acids (SCFAs). Overall, the fine-tuned regulation of vascular function is essential for cardiovascular homeostasis, and biologic-based therapies targeting NO signaling, Ca^{2+} modulation, and metabolic vascular regulation represent promising avenues for improving vascular health and reducing cardiovascular risk (Fig. 5).

Angiotensinogen

The renin–angiotensin–aldosterone system (RAAS) plays a pivotal role in the pathogenesis of hypertension. Angiotensin II, the primary effector molecule of the RAAS, increases blood pressure by directly or indirectly affecting vascular tone, blood volume, and electrolyte balance. This process ultimately promotes tissue remodeling and end-organ damage.[326] Angiotensin II exerts its

vasoconstrictive effects primarily through activation of the angiotensin II type 1 receptor. Upon receptor activation, the Gαq subunit directly stimulates phospholipase C, triggering the production of diacylglycerol and inositol trisphosphate.[327] This cascade induces intracellular Ca^{2+} mobilization, ultimately leading to vascular smooth muscle contraction and increased systemic vascular resistance. Given the central role of the RAAS in hypertension, RAAS inhibitors, particularly angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are integral to antihypertensive therapy.[328] However, a more advanced approach to targeting the RAAS is emerging—silencing hepatically derived angiotensinogen, the precursor protein of angiotensin II, through RNAi.[329,330] Compared with ACEIs and ARBs, targeting AGT theoretically offers a more comprehensive blockade of the RAAS, minimizing escape mechanisms while maintaining renal homeostasis and intact tubuloglomerular feedback, thereby enhancing both efficacy and safety.[331,332]

Zilebesiran, a siRNA that inhibits AGT synthesis, represents a groundbreaking advancement in this field. Zilebesiran, which is administered via subcutaneous injection, is currently being evaluated in multiple phase 2 clinical trials involving patients with hypertension. The KARDIA-1 trial,[330] a randomized, double-blind, placebo-controlled study conducted across 78 sites in four countries, enrolled 394 adults with mild to moderate hypertension. The primary endpoint was the change in mean systolic blood pressure (SBP) from baseline at 3 months. Zilebesiran significantly reduced SBP by 7.3–10 mmHg across the four dose groups, whereas the placebo group experienced an average SBP increase of 6.8 mmHg. Notably, a single dose of ≥200 mg of zilebesiran maintained an SBP reduction of over 10 mmHg for up to 6 months in hypertensive patients.[333] The KARDIA-2 study further demonstrated that zilebesiran, when added to standard antihypertensive therapy, achieved an additional reduction of 4–12 mmHg in the mean SBP without any new safety concerns.[334] To explore its potential in high-risk populations, the ongoing KARDIA-3 trial (NCT06272487) is enrolling cardiovascular high-risk patients or those with advanced chronic kidney disease who are taking 2–4 antihypertensive agents. This study aimed to assess the safety and efficacy of zilebesiran in this challenging patient population. Notably, the maximum blood pressure-lowering effect of zilebesiran occurs around week 8, making it unsuitable for the rapid correction of acute hypertensive crises. Nevertheless, the long-acting nature of zilebesiran, which requires only one injection every six months, makes it an especially attractive option for long-term hypertension management.[335]

Another promising approach for targeting AGT is antisense technology, represented by IONIS-AGT-LRx and ION-904. IONIS-AGT-LRx is an ASO that hybridizes with AGT mRNA, leading to its degradation via an RNase H1-dependent mechanism and a subsequent reduction in AGT protein production.[331,336] Data from three clinical studies (NCT04083222, NCT03714776, and NCT03101878) demonstrated that compared with placebo, IONIS-AGT-LRx significantly reduces plasma AGT levels, with good tolerability and no notable off-target effects.[331] Although reductions in systolic and diastolic blood pressure were observed in the treatment groups, these changes did not reach statistical significance, possibly due to the limited sample size and study power. To further investigate its antihypertensive potential, two additional clinical trials have been launched. The ASTRAAS trial (NCT04714320) evaluated changes in SBP from baseline to day 85 as the primary endpoint, whereas the ASTRAAS-HF trial (NCT04836182) investigated whether IONIS-AGT-LRx could serve as an adjunct therapy to standard treatment in patients with HFrEF. Both trials have recently concluded, but the results have not yet been disclosed. In addition, ION-904, developed by the same company as IONIS-AGT-LRx, aims to extend the duration of drug action, reducing the frequency of subcutaneous injections from weekly to monthly. Phase 1 clinical trials have confirmed that monthly subcutaneous injections of ION-904 safely and significantly reduce plasma AGT levels.[337] However, data on its antihypertensive efficacy have not yet been released (NCT05314439). Overall, the development of AGT-silencing biologics highlights an exciting new direction in hypertension management. With the potential for sustained efficacy, enhanced patient compliance, and superior safety, these agents could fill an important gap in the treatment landscape. The availability of ongoing clinical trials will provide critical data on their long-term efficacy, safety, and role in combination therapy with existing antihypertensive agents.

Natriuretic peptide receptor 1

Vascular function is a key determinant of blood pressure regulation, and targeting vasoconstriction and vasodilation remains a primary strategy for clinical blood pressure management. Among the key modulators of vascular tone, natriuretic peptides (NPs), including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), play crucial roles in promoting vasodilation and maintaining fluid homeostasis. ANP and BNP, both of which are secreted by the heart in response to hemodynamic stress, activate NPR1, a membrane-bound guanylyl cyclase receptor. NPR1 activation catalyzes the conversion of guanosine triphosphate to cGMP, which subsequently activates protein kinase G. This cascade reduces intracellular Ca^{2+} levels in VSMCs, leading to vasodilation.[338,339] Additionally, NPR1 signaling exerts pleiotropic cardiorenal benefits,[339,340] including natriuresis, diuresis, and vasorelaxation. Recent genetic analyses[341] and animal experiments[342] have confirmed the therapeutic potential of NPR1 as a novel target for hypertension management.[343]

Currently, three mAbs targeting NPR1—XXB750, REGN5381, and REGN7544—are undergoing clinical evaluation. Preliminary results from phase I clinical trials have shown that both XXB750[249] and REGN5381[344] significantly reduce SBP. XXB750 achieved a sustained SBP reduction of 8–16 mmHg, which was maintained for up to 28 days after administration. Similarly, REGN5381 was associated with reductions of 7–11 mmHg, with the antihypertensive effect persisting for up to 4 days. Notably, the monthly dosing regimen of XXB750 is currently being tested in an ongoing phase II clinical trial (NCT05562934), and if successful, this approach could significantly increase blood pressure control and patient adherence.

In addition to their role in hypertension, NPR1 agonists have gained attention in HF treatment because of their potential to improve hemodynamics and clinical symptoms.[345] However, the clinical use of recombinant natriuretic peptides, such as nesiritide, is limited because of their short duration of action. Cardiac natriuretic peptide. Recent innovations have aimed to address this limitation. In a clinical trial conducted in healthy adults, a single intravenous infusion of REGN5381 demonstrated sustained reductions in venous filling during the cardiac cycle, lowered stroke volume, and decreased cardiac output—effects that are critical for symptom management in heart failure patients.[346] Both XXB750 (NCT06142383) and REGN5381 (NCT05353166, NCT06237309) are currently being tested in phase II clinical trials for HF patients. These trials are expected to provide critical insights into the potential of NPR1-targeting biologics to improve HF outcomes. Moreover, REGN7544, which is still undergoing early-stage clinical evaluation, will also be assessed for its therapeutic potential in CVD (NCT05970718).

Relaxin/insulin-like family peptide receptor 1

Vascular dysfunction plays a pivotal role in the pathogenesis and progression of HF. Enhancing vasodilatory function to achieve hemodynamic improvement is a key therapeutic strategy for providing both symptomatic relief and long-term benefits for HF patients.[347,348] By reducing afterload, vasodilators improve

ventricular function and alleviate dyspnea by lowering cardiac filling pressures, making them a fundamental component of first-line HF therapy.[349] Relaxin-2, a peptide hormone secreted by the corpus luteum during pregnancy, binds primarily to RXFP1, modulating systemic hemodynamics and renal function to accommodate the increased cardiovascular load during pregnancy.[350] Preclinical studies have demonstrated that relaxin exerts vasodilatory, anti-inflammatory, and antifibrotic effects, highlighting its potential as a therapeutic option for HF.[351,352] Mechanistically, RXFP1 activation leads to Gαs coupling and adenylyl cyclase activation, thereby increasing intracellular cyclic adenosine monophosphate levels. This cascade further stimulates protein kinase A, which reduces intracellular Ca^{2+} concentrations, leading to vascular smooth muscle relaxation. Additionally, RXFP1 couples with Gβγ subunits to activate phosphoinositide 3-kinase (PI3K), which in turn phosphorylates protein kinase B (PKB/Akt), promoting endothelial nitric oxide synthase-mediated nitric oxide production and subsequent vasodilation.[353,354]

Serelaxin, a recombinant form of human relaxin-2 with an extended half-life of 7–8 h, is more suitable for therapeutic use than its endogenous counterpart.[355] Early-phase clinical studies have shown that serelaxin significantly improved dyspnea and postdischarge clinical outcomes in patients with acute HF.[355,356] However, the large-scale phase III RELAX-AHF-2 trial (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF) did not meet its primary endpoints. A study involving 6600 acute HF patients revealed that short-term administration of serelaxin did not reduce the proportion of patients with worsening HF on day 5 or cardiovascular mortality at 180 days.[357] This outcome may be attributed to the short treatment duration, which was insufficient to sustain beneficial hemodynamic effects.

To overcome the limitations of serelaxin, current research is focused on the development of novel long-acting relaxin analogs that can provide sustained hemodynamic benefits with reduced dosing frequency. LY3540378 (NCT05592275) and AZD3427 (NCT05737940) are currently in phase II clinical trials in HF patients. These biologics mimic the biological effects of endogenous relaxin but have significantly extended half-lives of 8–10 days[358] and 13–14 days,[359] respectively. This improvement in half-life is expected to prolong their therapeutic action, reduce dosing frequency, and enhance patient adherence. In addition to their role in hemodynamic regulation, relaxin analogs offer an added benefit in HF treatment—renal perfusion enhancement. To date, no approved treatment has been shown to directly improve renal function in chronic HF patients. By improving renal perfusion, relaxin analogs may address this critical clinical need, positioning themselves as potential game changers in HF management.

Gut microbiome and its metabolites

Emerging evidence suggests that gut microbiota dysbiosis plays a causative role in vascular dysfunction, highlighting the gut microbiome as a potential therapeutic target for hypertension.[360,361] Microbe-derived metabolites serve as key mediators of gut–host communication,[362,363] with SCFAs being among the most well characterized. SCFAs, including acetate, propionate, and butyrate, are produced in the colon through bacterial fermentation of dietary fiber and have been shown to significantly lower blood pressure in experimental models.[364–367] These effects are mediated through multiple pathways, including transcriptional reprogramming[365] and the activation of SCFA-sensitive G protein-coupled receptors (GPCRs), such as GPR41 and GPR43.[366] Upon receptor activation, Gβγ subunits trigger downstream signaling cascades that increase endothelial nitric oxide (NO) production, leading to vasodilation and improved vascular homeostasis. Additionally, SCFAs exert anti-inflammatory effects by modulating immune cell function, further contributing to their cardiovascular benefits.[368] Given these findings, therapeutic strategies aimed at modulating the gut microbiota composition or increasing SCFA bioavailability may represent a novel avenue for hypertension management and the prevention of end-organ damage.[365,366]

To further investigate the antihypertensive potential of SCFAs, a phase II randomized controlled trial was conducted to evaluate HAMSAB, a high-fiber supplement designed to produce high levels of acetate and butyrate. The trial included patients with untreated essential hypertension.[369] The results demonstrated a significant and clinically relevant reduction in 24-h SBP, independent of age, sex, and body mass index. The mean difference in SBP reduction relative to placebo was −6.1 mmHg, a reduction associated with a 10% decrease in the relative risk of major cardiovascular events.[370] Given these promising results, the next step is to evaluate the efficacy of HAMSAB in patients with resistant hypertension, a population that fails to respond to traditional monotherapy or combination antihypertensive regimens and thus requires novel therapeutic options.[371]

In addition to SCFAs, fecal microbiota transplantation[372] (NCT05608447) and washed microbiota transplantation[373] are being actively explored for their potential to modulate blood pressure. In addition to SCFAs, other gut-derived metabolites, including bile acids,[374–376] trimethylamine N-oxide[377–380] and indole-3-lactic acid,[380] have been linked to the pathogenesis of hypertension. Animal studies have revealed significant associations between these metabolites and blood pressure regulation. However, causal relationships have yet to be established, and further investigation is needed to confirm their therapeutic potential. To facilitate this transition from observational findings to clinical application, large-scale randomized clinical trials are essential.

Further randomized clinical trials are urgently needed to transition from observational associations to causal relationships and ultimately promote the therapeutic application of these metabolites. Future studies should prioritize the synergistic effects of gut microbial interventions with traditional antihypertensive drugs. Precision microbiome analysis could enable the development of personalized antihypertensive strategies, paving the way for microbiome-guided precision medicine in hypertension management. Such approaches may not only enhance treatment efficacy but also open new avenues for combating drug-resistant hypertension.

Limitations and perspectives

Therapies targeting vascular function effectively reduce hypertension and improve hemodynamics. In this context, RAAS inhibition therapy using small nucleotides or NRP1 activators has demonstrated success, as it directly counteracts the long-term RAAS activation responsible for vascular and cardiac remodeling. However, their mixed outcomes in clinical trials for HF suggest that benefits may be limited to slowing rather than reversing pathological remodeling processes (Table 1). This implies that such biologics may be effective only when they are administered preventively. Reversing established pathological remodeling to treat symptomatic HF remains a critical unmet therapeutic challenge.

LIPID METABOLISM MODULATION

Dysregulation of lipid metabolism plays a pivotal role in the pathogenesis and progression of atherosclerosis and ASCVD. LDL-C is a well-established causal factor in ASCVD, while elevated triglyceride (TG)-rich lipoproteins and lipoprotein(a) [Lp(a)] have also been strongly linked to increased cardiovascular risk. As a result, lowering plasma LDL-C, TG, and Lp(a) levels has become a central strategy in ASCVD prevention and treatment,[381] with biologic therapies significantly transforming the lipid-lowering landscape. Biologics modulation of lipid metabolism primarily

Table 1. Summary of biologics used for cardiac regeneration, reverse cardiac remodeling, genetic cardiomyopathy, and vascular function modulation

Objective	Target	Drug	Classification	Developer	Indication	Phase	Identifier
Cardiac regeneration	PSC-CM	HS-001	Cell	Heartseed	Heart failure	I/II	NCT04945018
		EHM[48]	Cell	University Medical Center Goettingen	Heart failure	I/II	NCT04396899
		iPSC-CL[64]	Cell	HeartWorks	Congenital Heart Disease	I	NCT05647213
		hESC-CMs	Cell	Stanford University	Chronic ischemic left ventricular dysfunction	I/II	NCT05068674
		HiCM-188[49]	Cell	Help Therapeutics	Heart failure	I/II	NCT06340048, NCT03763136, NCT05566600, NCT05223894,
	NRG1/ErbB	Neucardin	Recombinant protein	Zensun Sci & Tech	Heart failure	III	NCT03388593, NCT05949801, CTR20230733, NCT04468529
		JK07	Fusion protein	Salubris Biotherapeutics	Heart failure	II	NCT06369298, NCT04210375
	VEGF-A	AZD8601	mRNA	AstraZeneca	Heart failure	II	NCT03370887
	EVs	PEP	EVs	Mayo Clinic	Percutaneous coronary intervention	I	NCT04327635
		Mitochondria and MSC-derived exosomes	EVs	Tehran University of Medical Sciences	Coronary artery bypass grafting	I/II	NCT05669144
		EVs of iPSC-CPCs	EVs	Assistance Publique - Hôpitaux de Paris	Nonischemic cardiomyopathies	I	NCT05774509
Cardiac reverse remodeling	IL-1	Rilonacept[164–166]	Fusion protein	Kiniksa	Recurrent Pericarditis	Approved	NCT03737110, NCT03980522
		Goflikicept[161,167,172]	Fusion protein	R-Pharm	Recurrent Pericarditis, STEMI	III	NCT04692766, NCT05673902, NCT04463251
	IL-6	Ziltivekimab[177–179]	mAb	Novo Nordisk	ASCVD	III	NCT03926117, NCT04626505, NCT05021835,
	GLP-1	Liraglutide[186,191,193,205,206]	Peptide	Novo Nordisk	CVDs with T2D	Approved	NCT01794143, NCT01179048
		dulaglutide[200–203]	Peptide	Eli Lilly	CVDs with T2D	Approved	NCT01394952, NCT05390892
		Semaglutide[187,207–209]	Peptide	Novo Nordisk	CVDs with either obesity or overweight	Approved	NCT03574597, NCT03819153, NCT04788511, NCT04916470
		tirzepatide[212,213]	Peptide	Eli Lilly	CVDs with T2D or obesity	Approved	NCT04255433, NCT04847557
	miR-132	CDR132L[467]	ASO	Cardior	Heart failure	II	NCT04045405, NCT05350969
	miR-92a	MRG-110[228]	ASO	miRagen Therapeutics	Heart failure	I	NCT03603431
	SERCA2a	SRD001	AAV-GRT	Sardocor	Heart failure	I/II	NCT04703842, NCT06061549
		MYDICAR[243–245]	AAV-GRT	Celladon	Heart failure	II	NCT01966887, NCT00534703, NCT01643330, NCT00454818
	I-1	AB1002	AAV-GRT	Asklepios Bio	Heart failure	II	NCT05598333, NCT04179643
	AC6	RT100[251,252]	AAV-GRT	Renova Therapeutics	Heart failure	II/III	NCT00787059, NCT03360448
Genetic cardiomyopathy	TTR	NI006[273,274]	mAb	Neurimmune & Alexion	ATTR-CM	III	NCT04360434, NCT06183931
		PRX004[270]	mAb	Novo Nordisk	ATTR-CM	II	NCT03336580, NCT05442047
		Patisiran[278]	siRNA	Alnylam	hATTR-PN	Approved	NCT01960348, NCT03997383, NCT02510261
		Vutrisiran[280]	siRNA	Alnylam	hATTR-PN	Approved	NCT04153149, NCT03759379
		Inotersen[281,282]	ASO	Ionis	hATTR-PN	Approved	NCT03702829, NCT01737398,
		Eplontersen[284–286]	ASO	Ionis & AstraZeneca	hATTR-PN	Approved	NCT03728634, NCT04136184, NCT04136171
		NTLA-2001[289,468]	CRISPR-Cas9	Intellia	ATTR-CM	III	NCT06128629
	PKP2	TN-401	AAV-GRT	Tenaya	ARVC	I	NCT06228924
		LX2020	AAV-GRT	Lexeo	ARVC	I/II	NCT06109181
		RP-A601	AAV-GRT	Rocket Pharmaceuticals	ARVC	I	NCT05885412

Table 1. continued

Objective	Target	Drug	Classification	Developer	Indication	Phase	Identifier
	MYBPC3	TN201	AAV-GRT	Tenaya	HCM	I	NCT05836259
	LAMP2B	RP-A501[316]	AAV-GRT	Rocket Pharmaceuticals	HCM	II	NCT03882437, NCT06092034
Vascular function modulation	AGT	Zilebesiran[330]	siRNA	Alnylam	Hypertension	II	NCT04936035, NCT06272487, NCT05103332
		IONIS-AGT-LRx[331]	ASO	Ionis	Hypertension, heart failure	II	NCT04714320, NCT04836182
		ION-904	ASO	Ionis	Hypertension	II	NCT04731623, NCT05314439
	NPR1	XXB750	mAb	Novartis	Hypertension, heart failure	II	NCT05562934, NCT05328752, NCT06142383
		REGN5381[344]	mAb	Regeneron	Heart failure	II	NCT05353166, NCT06237309
		REGN7544	mAb	Regeneron	Pending	I	NCT05970718
	RXFP1	Serelaxin[357]	mAb	Novartis	Heart failure	Approved	NCT01870778
		AZD3427[359]	mAb	AstraZeneca	Heart failure	II	NCT05592275, NCT04630067
		LY3540378[358]	mAb	Eli Lilly	Heart failure	II	NCT05737940, NCT04768855
	Gut microbiome	HAMSAB[369]	Prebiotic	Monash University	Hypertension	II	ACTRN12619000916145

PSC-CM pluripotent stem cell-derived cardiomyocyte, *NRG1/ErbB* Neuregulin 1-erbB, *VEGF-A* vascular endothelial growth factor A, *IL-1* interleukin-1, *IL-6* interleukin-6, *GLP-1* glucagon-like peptide-1, *SERCA2a* Sarcoplasmic/endoplasmic reticulum Ca2 + -ATPase 2a, *I-1* protein phosphatase inhibitor 1, *AC6* adenylyl cyclase 6, *TTR* transthyretin, *PKP2* Plakophilin 2, *MYBPC3* cardiac myosin-binding protein C3, *LAMP2B* lysosomal-associated membrane protein 2b, *AGT* angiotensinogen, *NPR1* natriuretic peptide receptor 1, *RXFP1* relaxin/insulin-like family peptide receptor 1, *mAb* monoclonal antibody, *ASO* antisense oligonucleotide, *AAV-GRT* Adeno-associated virus-based gene replacement therapy, *siRNA* small interfering RNA, *STEMI* ST segment elevated acute myocardial infarction, *ASCVD* atherosclerotic cardiovascular diseases, *CVD* cardiovascular diseases, *T2D* type 2 diabetes, *ATTR-CM* transthyretin amyloid cardiomyopathy, *hATTR-PN* hereditary transthyretin amyloidosis

operates through two fundamental mechanisms: (1) enhancing hepatic clearance of lipoproteins via upregulation of low-density lipoprotein receptor (LDLR) activity and (2) directly altering the composition, modification, and metabolism of atherogenic lipoproteins.[22] PCSK9 inhibitors function by preventing LDLR degradation, thereby increasing hepatic LDL-C clearance and reducing plasma LDL-C concentrations,[382] representing a major breakthrough in lipid-lowering strategies. Regulatory targets for modifying atherogenic lipoproteins include ANGPTL3, apolipoprotein C3 (apoC3), cholesteryl ester transfer protein (CETP), lipoprotein(a) (Lp(a)), and high-density lipoprotein (HDL). Since their mechanisms of action are independent of LDLR pathways, associated therapeutics offer potential treatments for populations lacking functional LDLRs, such as those with homozygous familial hypercholesterolemia (HoFH). Biologic lipid-modulating therapies are evolving beyond lowering LDL-C to encompass interventions targeting triglyceride-rich lipoproteins (TRLs), Lp(a), and HDL metabolism. The development of RNA interference, monoclonal antibodies, and vaccine-based approaches is driving innovation in this field (Fig.6; Table 2).

Proprotein convertase subtilisin/kexin type 9

LDL-C is both a causal factor and a cumulative factor in the development of atherosclerosis. Consequently, reducing plasma LDL-C levels, regardless of the method used, significantly lowers the risk of CVD.[383,384] PCSK9 is a key regulator of LDLR homeostasis and mediates LDLR degradation in hepatocytes. PCSK9 inhibitors, including monoclonal antibodies and RNA-based therapies, represent groundbreaking advancements, reshaping the LDL-C-lowering drug landscape.[385] Four biologics have received clinical approval, including three mAbs— evolocumab, alirocumab, and tafolecimab—and one small interfering RNA (siRNA) drug, inclisiran. These therapies represent major milestones in cardiovascular medicine. Notably, after a median follow-up of 2.2 years and 2.8 years, respectively, evolocumab and alirocumab were shown to reduce the relative risk of MACEs by 15%.[386,387] Furthermore, recent findings from the FOURIER-OLE and ODYSSEY Outcomes studies have underscored the long-term safety and tolerability of PCSK9 mAbs for up to 8 years, emphasizing the importance of early treatment initiation.[388,389] Other PCSK9 mAbs, such as ebronucimab, recaticimab, and ongericimab, are currently under active development, expanding the array of treatment options available.

In addition to mAbs, the third generation of PCSK9 inhibitors includes oral peptides, fusion proteins, vaccines and gene-editing therapies, all of which are at various stages of development.[390] Lerodalcibep, a recombinant fusion protein that binds the PCSK9 binding domain to human serum albumin, has demonstrated efficacy comparable to that of PCSK9 mAbs in phase III clinical trials.[18] Lerodalcibep offers several advantages over mAbs, including a longer half-life, lower injection frequency, and easier synthesis and storage at ambient temperatures, which could substantially improve accessibility, especially in resource-limited healthcare settings.[391] Moreover, PCSK9-targeting vaccines aim to provide sustained effects through immune memory. However, early-phase I trials in humans and nonhuman primates have shown that their ability to lower LDL-C remains suboptimal.[392–394]

Given the lifelong nature of lipid-lowering therapy, gene-editing technologies that enable permanent suppression of therapeutic targets may offer transformative benefits for managing chronic diseases. One such therapy is VERVE-101, a CRISPR-based gene-editing treatment for PCSK9. It delivers mRNA encoding an adenine base editor and guide RNA via LNPs to introduce permanent changes in the PCSK9 gene.[395,396] HEART-1, the world's first-in-human clinical trial of in vivo base editing, aims to validate the potential of PCSK9 base editing to achieve sustained reductions in LDL-C. The interim results presented in the 2023 American Heart Association Scientific Sessions were

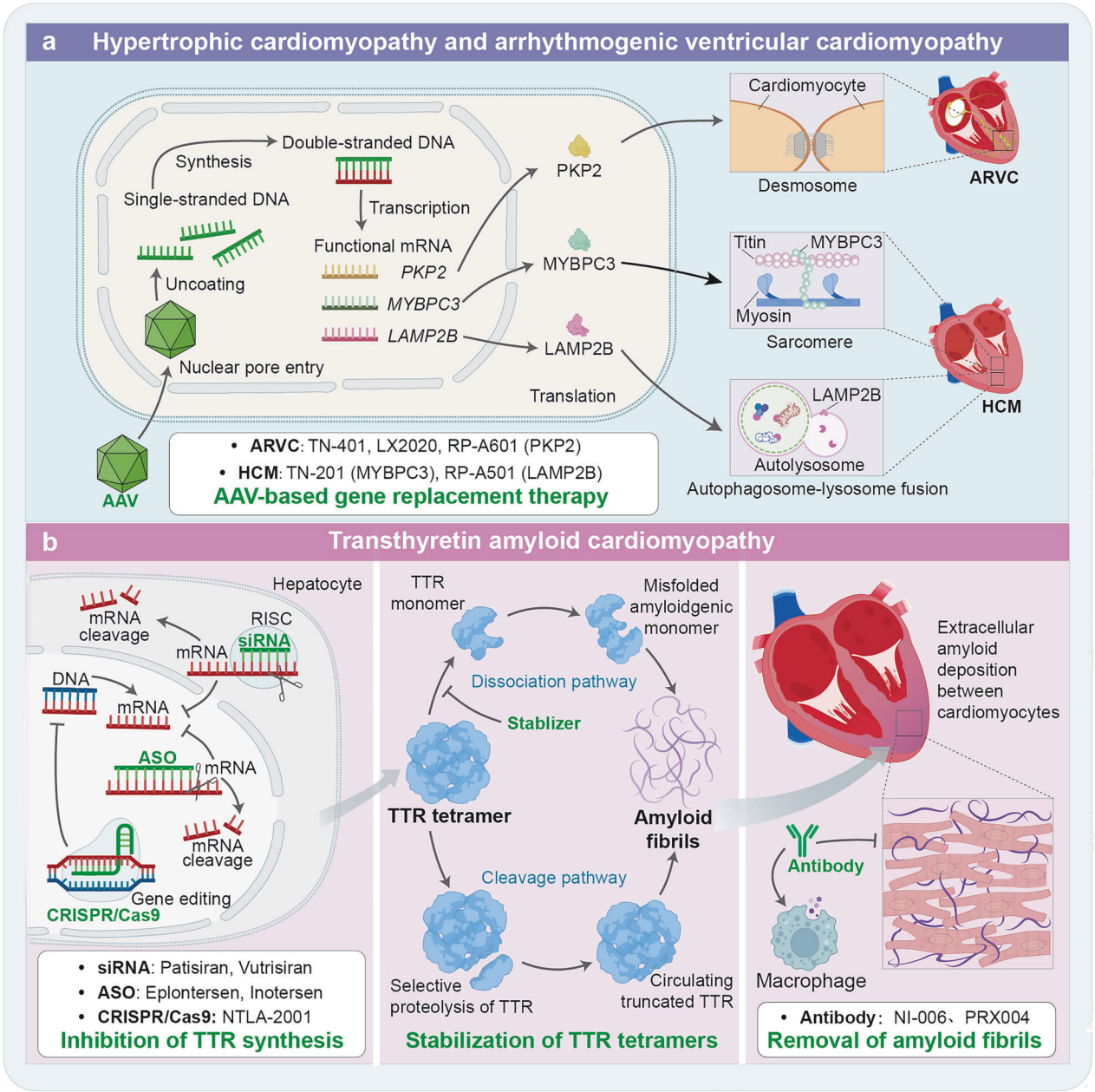

Fig. 4 Therapeutic strategies and mechanisms in genetic cardiomyopathies. **a** AAV-based gene replacement therapy represents a promising approach for treating HCM and ARVC. Upon nuclear pore entry, AAV virions undergo uncoating, releasing the viral genome into the nucleus. Single-stranded AAV DNA is then converted into a double-stranded form, initiating transcription, nuclear export of mRNA, and subsequent translation of the target protein. In ARVC, mutations in PKP2 constitute the predominant desmosomal gene abnormalities, contributing to the structural instability of cardiomyocytes. In HCM, mutations in MYBPC3 are the most frequent genetic cause, leading to sarcomere disarray and pathological hypertrophy. Additionally, LAMP2B mutations disrupt autophagosome–lysosome fusion, inducing cellular stress responses and exacerbating HCM pathology. Gene replacement therapy aims to restore normal protein levels, thereby halting or even reversing disease progression. **b** TTR is synthesized by the liver and typically circulates as a homotetramer. It dissociates or is proteolytically cleaved into intermediates that misfold and ultimately aggregate into amyloid fibrils. Amyloid fibrils then deposit in the heart, resulting in heart failure. Treatment of ATTR cardiomyopathy includes inhibition of TTR synthesis, stabilization of TTR tetramers and removal of amyloid fibrils. AAV adeno-associated virus, HCM hypertrophic cardiomyopathy, ARVC arrhythmogenic right ventricular cardiomyopathy, PKP2 plakophilin 2, MYBPC3 myosin-binding protein C3, LAMP2B lysosome-associated membrane protein 2, TTR transthyretin, ASO antisense oligonucleotide, siRNA small interfering RNA (Created with BioRender.com)

groundbreaking. Patients receiving the highest dose (0.6 mg/kg) of VERVE-101 achieved a 55% reduction in LDL-C at 1 month, with persistently low cholesterol levels observed 6 months after treatment. This remarkable result earned HEART-1 recognition as one of the "11 most influential clinical trials shaping the future of medicine in 2024".[397]

Despite these promising results, safety concerns remain a major hurdle for VERVE-101. Two patients experienced three serious adverse events, including MI, which was potentially related to the treatment. In response, researchers have halted enrollment in the HEART-1 trial[398] and shifted their focus to VERVE-102, a next-generation formulation with the same active components as

VERVE-101 but employing a new ionizable lipid for LNP delivery. This lipid has shown better safety and tolerability in other clinical trials. The HEART-2 trial (NCT06164730) will evaluate the safety and efficacy of VERVE-102. Furthermore, gene-editing therapies targeting Angiopoietin-like 3 (ANGPTL3)[399,400] and LDLR[401,402] have entered the preclinical stage, highlighting the broader potential of gene-editing-based lipid-lowering strategies, and long-acting therapies that provide stable and durable lipid-lowering effects could further reduce the risk of cardiovascular events.[403]

Angiopoietin-like 3

By inhibiting ANGPTL3, the activity of lipoprotein lipase (LPL) is increased, facilitating the clearance of TRLs and resulting in a reduction in the circulating levels of LDL-C and triglycerides .[404,405] Evinacumab, a monoclonal antibody targeting ANGPTL3, received FDA and European Medicines Agency (EMA) approval in 2021 for the treatment of HoFH. Owing to its proven efficacy and safety,[406] the FDA expanded its indication in 2023 to include children aged 5–11 years with HoFH, marking an important milestone in the treatment of pediatric lipid disorders.

Long-term treatment with inclisiran has validated the safety and effectiveness of siRNA therapy for dyslipidemia,[407] significantly advancing drug development at the RNA level. Several siRNA-based ANGPTL3 inhibitors have entered phase II clinical trials and have demonstrated promising efficacy and safety profiles. One notable example is Zodasiran, which has shown encouraging results in the ARCHES-2 trial.[408] Preliminary analysis revealed favorable changes in serum lipid and lipoprotein levels, supporting the potential of zodasiran to reduce CVD risk. Moreover, zodasiran exhibited a favorable safety profile, underscoring its potential as a novel approach for lipid management.

Apolipoprotein C3

Like ANGPTL3, APOC3 serves as a crucial regulator of lipid metabolism by inhibiting the activity of LPL. However, the proatherogenic effects of elevated circulating APOC3 are not solely dependent on LPL inhibition. APOC3 also impairs the apoE-mediated clearance of TRLs by hepatic receptors, leading to elevated TRL levels in the blood.[409,410] This dual mechanism distinguishes APOC3 from ANGPTL3, particularly in the context of LPL-deficient patients. In such cases, APOC3-targeted therapies may offer greater efficacy since ANGPTL3 inhibition relies on LPL-dependent pathways.[411] Genetic studies have further reinforced this therapeutic rationale, as loss-of-function mutations in the APOC3 gene are associated with lower plasma triglyceride levels and a reduced risk of ASCVDs.[412,413]

Biologics that target APOC3 have shown remarkable efficacy in clinical trials. Volanesorsen, an ASO, was conditionally approved by the EMA in August 2019 for the treatment of familial chylomicronemia syndrome, a rare genetic disorder characterized by severe hypertriglyceridemia. However, owing to concerns about off-target effects and the risk of thrombocytopenia, caution is needed when this therapy is prescribed.[414] To overcome these limitations, Olezarsen, a next-generation ASO with enhanced liver-targeting properties conferred by a GalNAc moiety, was developed.[415] The improved hepatocyte specificity of Olezarsen enhances its safety profile and expands its lipid-modifying potential beyond familial chylomicronemia.[416,417]

Recent clinical trials have validated the efficacy and safety of Olezarsen. In the Bridge-TIMI 73a study involving patients with hypertriglyceridemia and the BALANCE study focusing on patients with familial chylomicronemia syndrome, Olezarsen significantly lowered plasma triglyceride levels without causing major safety issues.[417,418] These findings support the potential for regulatory approval and broader clinical applications of Olezarsen, setting the stage for expanded use in managing hypertriglyceridemia. In addition to ASO therapies, siRNA drugs targeting APOC3 are rapidly advancing in clinical development. One prominent candidate is Plozasiran, which has reached the phase II SHASTA-2 clinical trial.[419] The trial results demonstrate that Plozasiran can significantly and sustainably reduce triglyceride and TRL levels, with favorable safety and tolerability profiles. However, while these outcomes are promising, the comprehensive effects of plozasiran on atherogenic lipoproteins and its impact on ASCVD risk remain to be explored in larger-scale clinical trials.

Lipoprotein(a)

Elevated Lp(a) is a well-established causal risk factor for ASCVD.[420–422] A recent study revealed that higher Lp(a) concentrations correlate with premature development and increased severity of coronary artery disease in acute coronary syndrome patients.[423] The atherogenic, proinflammatory and prothrombotic properties of Lp(a) contribute to its role in ASCVD pathogenesis[424] Notably, 70–90% of the serum Lp(a) concentration is genetically determined by the expression of the LPA gene[425,426] and is largely unaffected by diet and lifestyle modifications.[427] Epidemiological studies estimate that approximately 20% of the general population has genetically elevated Lp(a) levels, predisposing them to a higher lifetime risk of ASCVD.[428]

Current lipid-lowering therapies, such as statins and PCSK9 inhibitors, have minimal effects on Lp(a) levels,[429] necessitating the development of novel therapeutics to target Lp(a) directly. Recent advances in RNA therapeutics have led to the development of ASOs and siRNA drugs targeting LPA mRNA. One such agent is pelacarsen, an ASO conjugated with GalNAc to enable efficient hepatocyte delivery and prolonged action.[430,431] In a phase II clinical trial involving 286 ASCVD patients with elevated Lp(a) levels,[432] 98% of patients receiving high-dose pelacarsen achieved the Lp(a) levels recommended by the European[433] and North American [434]guidelines.

Compared with ASO-based drugs, siRNA therapeutics that target LPA mRNA, such as olpasiran, zerlasiran, and lepodisiran, offer unique advantages. The mechanism of action of siRNA enables longer-lasting effects and lower dosing frequencies than ASO-based therapies do.[435] Additionally, preliminary clinical evidence suggests that these siRNA agents may achieve greater Lp(a) reduction than ASOs do, potentially providing greater cardiovascular benefits.[432,436–438] However, key uncertainties remain. The most critical question is whether a reduction in Lp(a) alone—independent of its impact on other lipid parameters—can significantly lower the risk of cardiovascular events. This fundamental question is being addressed in several large-scale cardiovascular outcome trials. Notably, the Lp(a)HORIZON (NCT04023552), OCEAN(a) (NCT04606602) and ACCLAIM-Lp(a) (NCT05581303) trials are currently underway. These trials aim to determine whether the substantial reduction in Lp(a) achieved by RNA therapies can translate into clinical benefits, including reductions in MACEs. The outcomes of these landmark studies will be pivotal in shaping the future of Lp(a)-targeted therapies. If successful, they could offer a novel pathway for ASCVD risk reduction.

High-density lipoprotein and cholesteryl ester transfer proteins

HDL has long been considered an attractive therapeutic target because of its critical role in reverse cholesterol transport and its well-documented anti-inflammatory and antioxidant properties.[439,440] Epidemiological studies have consistently shown an inverse correlation between HDL-C levels and ASCVD risk,[441,442] leading to the hypothesis that increasing HDL-C levels could reduce cardiovascular events. However, clinical trials targeting HDL-C elevation have yielded disappointing results, failing to demonstrate a significant reduction in cardiovascular events.[443,444] A prime example is CSL112, a reconstituted human apoA-I infusion,[445] which aims to increase cholesterol efflux capacity, a key mechanism by which HDL facilitates reverse cholesterol

Table 2. Summary of emerging lipid-modulating biologics

target	Drug	Type	Phase	Developer	Additional notes/reference
PCSK9	Inclisiran	siRNA	Phases 3 to 4	Novartis	ORION-4 trial is ongoing to test effects on MACE. (NCT03705234)
	Alirocumab	mAb	Phase 4	Regeneron	Reduced the risk of MACE with an HR of 0.85.[386]
	Rvolocumab	mAb	Phase 4	Amgen	Reduced the risk of MACE with an HR of 0.85.[387]
	Tafolecimab	mAb	Phases 3 to 4	Innovent Biologics	EMPACT trial is ongoing to test its effects on MACE. (NCT06096909)
	Ebronucimab	mAb	Phase 3	Akeso Biopharma	NMPA accepted its NDA in June 2023.
	Recaticimab	mAb	Phase 3	Jiangsu Hengrui	NMPA accepted its NDA in June 2023.
	Lerodalcibep	Recombinant protein	Phase 3	LIB Therapeutics	BLA and MAA were filed in 2023.
	Ongericimab	mAb	Phase 3	Junshi Biosciences	NMPA accepted its NDA in April 2023.
	CiVi-007	ASO	Phase 2	CiVi Biopharma	Phase II trial completed in 2020, but no results published. (NCT04164888)
	RBD 7022	siRNA	Phase 1	Ribo Life Science	Phase I trial is ongoing. (NCT05912296)
	SGB-3403	siRNA	Phase 1	Sanegene Bio	Phase I trial is ongoing. (NCT06239714)
	SAL-003	mAb	Phase 2	Salubris Pharmaceuticals	Phase II trial is ongoing (CTR20230897)
	AT04A	Peptide Vaccine	Phase 1	Affiris	Phase I trial was completed, proving its developmental potential.[392]
	VXX-401	Peptide Vaccine	Phase 1	Vaxxinity	Phase I trial is ongoing. (NCT05762276)
	VERVE-101	Gene editing	Phase 1	Verve Therapeutics	The results of the phase I trial showed safety and efficacy.[396] (NCT05398029)
	SYH2053	siRNA	Phase 1	CSPC Pharmaceutical Group	Phase I trial is ongoing in China. (CTR20234189)
ANGPTL3	Evinacumab	mAb	Phases 3 to 4	Regeneron	FDA has extended its approval to children aged 5 to 11 with HoFH.
	Solbinsiran	siRNA	Phase 2	Eli Lilly	Phase II trial is ongoing. (NCT05256654)
	Zodasiran	siRNA	Phase 2	Arrowhead Pharmaceuticals	The results of the phase 2b trial showed safety and efficacy. (NCT04832971)
	VSA003	siRNA	Phase 2	Visirna Therapeutics	Visirna Announced Breakthrough Therapy Designation Granted in January 2024, but no clinical data has been reported. (NCT05851066)
	NNC0491-6075	mAb	Phase 1	Novo Nordisk	Phase I trial is ongoing. (NCT05979428)
	SHR-1918	mAb	Phase 2	Jiangsu Hengrui	Phase II trial is ongoing. (NCT06109831)
	JS401	siRNA	Phase 1	Junshi Biosciences	Phase I trial is ongoing. (NCT06041165)
APOC3	Volanesorsen	ASO	Phase 3 to 4	Akcea Therapeutics	In August 2019, volanesorsen was conditionally approved by the EMA for FCS. Due to the risk of thrombocytopenia, it should be used with caution.[414]
	Olezarsen	ASO	Phase 3	Akcea Therapeutics	BLA and MAA were filed in 2024.
	Plozasiran	siRNA	Phase 3	Arrowhead Pharmaceuticals	Phase III trial are ongoing. (NCT05089084, NCT06347003, NCT06347133, NCT06347016)
	LY-3875383	siRNA	Phase 1	Eli Lilly	Phase I trial was completed recently. (NCT05609825)
	STT-5058	mAb	Phase 1	Staten Biotechnology	Phase I trial was terminated for the recruitment failure. (NCT04419688)
	VSA001	siRNA	Phase 3	Visirna Therapeutics	Phase III trial is ongoing, but no result has been reported. (NCT05902598)
	RBD 5044	siRNA	Phase 1	Suzhou Ribo Life Science	Phase I trial is ongoing. (NCT05539651)
Lp(a)	Pelacarsen	ASO	Phase 3	Novartis	Lp(a)HORIZON trial is ongoing to test effects on MACE. (NCT04023552)
	Olpasiran	siRNA	Phase 3	Amgen	OCEAN(a) trial is ongoing to test effects on MACE. (NCT05581303)
	Zerlasiran	siRNA	Phase 2	Silence Therapeutics	Phase II trial has completed enrollment. (NCT05537571)
	Lepodisiran	siRNA	Phase 3	Eli Lilly	ACCLAIM-Lp(a) trial is ongoing to test effects on MACE. (NCT06292013)
HDL-C	CSL112	Recombinant protein	Phase 3	Commonwealth Serum Laboratories	No significant MACE reduction was observed from the AEGIS-IItrial.[443]
	MEDI-6012	Recombinant protein	Phase 2	MedImmune	Disappointing results were announced from the REAL-TIMI 63B trial.[444]
CETP	HB-ATV-8	Peptide Vaccine	Preclinical	National Autonomous University of Mexico	Valuable preclinical data was published.[452,469]
	Lip-CETP	Peptide Vaccine	Preclinical	Mashhad University of Medical Sciences	Lip-CETP showed a strong atheroprotective effect in rabbit model.[453]

PCSK9 proprotein convertase subtilisin/kexin type 9, *ANGPTL3* Angiopoietin-like 3, *ApoC3* apolipoprotein C3, *Lp(a)* lipoprotein(a), *CETP* cholesteryl ester transfer protein, *HDL-C* high-density lipoprotein-cholesterol, *MACE* major adverse cardiovascular event, HR hazard ratio, *NMPA* National Medical Products Administration, *NDA* new drug application, *BLA* biologics license application, MAA marketing authorization application, *FDA* Food and Drug Administration, *HoFH* homozygous familial hypercholesterolemia, *EMA* European Medicines Agency, *FCS* familial chylomicronemia syndrome

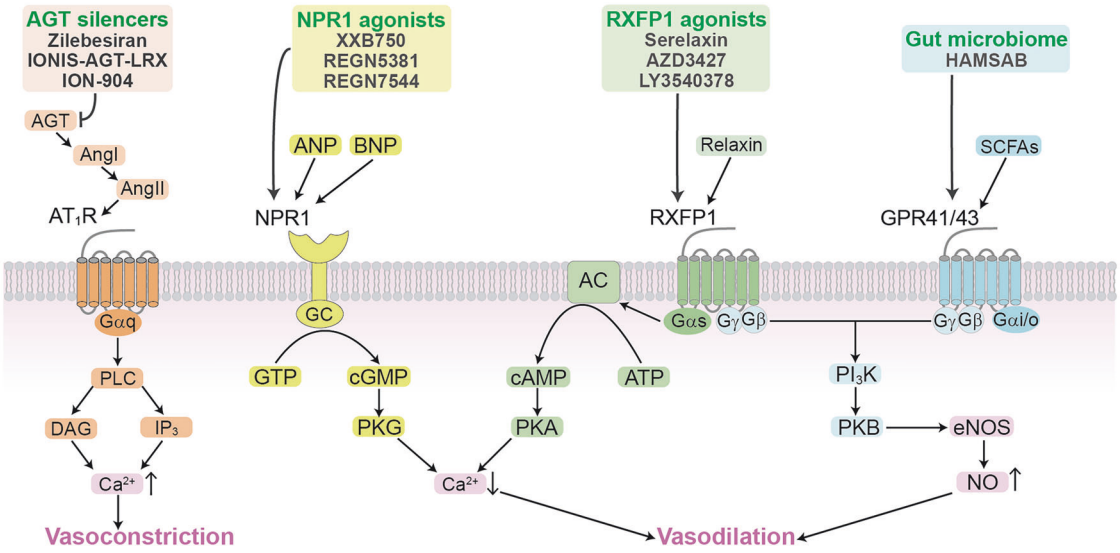

Fig. 5 Targets and mechanisms regulating vascular function. Ang II is a potent vasoconstrictor that exerts its effects through activation of AT1R. The Gαq subunit directly activates PLC, leading to the production of DAG and IP_3, which ultimately induce vasoconstriction via an increase in their intracellular levels. Silencing of hepatically derived AGT, the precursor of Ang II, attenuates Ang II production, thereby lowering blood pressure and inducing vasodilation. ANP and BNP, both secreted by the heart, activate NPR1, a membrane-bound guanylyl cyclase receptor, along with NPR1-agonistic monoclonal antibodies. Upon activation, NPR1 catalyzes the conversion of GTP to cGMP, which subsequently activates PKG, leading to a reduction in its intracellular level and promoting vasodilation. Relaxin, which is primarily secreted by the corpus luteum, binds to RXFP1, leading to Gαs coupling and the activation of AC, thereby increasing intracellular cAMP levels. This cascade further activates PKA, ultimately reducing intracellular Ca^{2+} levels. Additionally, RXFP1 couples with Gβγ subunits to activate PI3K, which in turn activates PKB, facilitating eNOS-mediated NO production and subsequent vasodilation. RXFP1-agonistic monoclonal antibodies leverage this signaling cascade to improve hemodynamic function. SCFAs, which are metabolites derived from the gut microbiota, act on GPR41 and GPR43, both of which are GPCRs. Their activation leads to Gβγ-mediated signaling, ultimately enhancing NO production and promoting vasodilation. Ang II Angiotensin II, AT1R angiotensin II type 1 receptor, PLC phosphendothelial nitric oxide synthaseolipase C, DAG diacylglycerol, IP_3 inositol triphosphate, AGT angiotensinogen, ANP atrial natriuretic peptide, BNP, brain natriuretic peptide, NPR1 natriuretic peptide receptor 1, PKG protein kinase G, RXFP1 relaxin/insulin-like family peptide receptor 1, AC adenylyl cyclase, PKA protein kinase A, PI3K phosphoinositide 3-kinase, PKB protein kinase B, eNOS endothelial nitric oxide synthase, SCFAs short-chain fatty acids, GPR41 G protein-coupled receptor 41, GPR43 G protein-coupled receptor 43, GPCRs G protein-coupled receptors (Created with BioRender.com)

transport. The AEGIS-II trial, which enrolled 18,219 patients with AMI, tested whether CSL112 could reduce the incidence of MACEs, including MI, stroke, and cardiovascular death.[443] Unfortunately, the trial results showed that CSL112 did not significantly reduce the composite primary endpoint, challenging the longstanding hypothesis that direct enhancement of HDL function would provide clinical benefits. These findings prompted further reflection on the role of HDL as a therapeutic target and raised critical questions about whether strategies aimed at increasing HDL-C or promoting cholesterol efflux are still viable.[443,446]

Unlike HDL, targeting CETP offers a distinct therapeutic strategy. CETP facilitates the transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoproteins, effectively lowering HDL-C and increasing LDL-C.[447] CETP inhibition, therefore, has the potential to reduce LDL-C while increasing HDL-C, a dual benefit in the context of ASCVD prevention.[383] However, the development of CETP inhibitors has faced numerous setbacks,[448,449] with several high-profile drug candidates, such as torcetrapib, dalcetrapib, and evacetrapib, failing in phase III clinical trials owing to either a lack of efficacy or off-target adverse effects. Despite these challenges, obicetrapib has emerged as a promising CETP inhibitor with favorable safety and efficacy profiles.[450,451] If successfully approved, obicetrapib could revive interest in CETP as a therapeutic target and reinvigorate efforts to develop CETP-targeting biologics. CETP-targeted vaccines have also shown promise in preclinical studies. Two leading vaccine candidates, Lip-CETP and HB-ATV-8, have demonstrated significant atherosclerotic plaque reduction and cardiovascular protection in animal models.[452,453] Unlike traditional small-molecule inhibitors, CETP vaccines could offer a more cost-effective and long-lasting treatment approach by leveraging the body's immune system to maintain therapeutic efficacy over extended periods.

Limitations and perspectives

Despite the transformative potential of biologic therapies for modulating lipid metabolism, such as PCSK9 inhibitors for lowering LDL-C and emerging RNA-based agents that target Lp(a) and triglycerides, significant limitations still remain. In addition to residual cardiovascular risk despite aggressive LDL reduction, high costs limiting accessibility, and unresolved long-term safety concerns, past failures of HDL-directed therapies such as CETP inhibitors underscore the complexity of lipid biology. Next-generation lipid management strategies will need to employ precision-guided, multitarget interventions to address the complex pathophysiology of lipid-mediated cardiovascular disease comprehensively.

CONCLUSIONS AND PERSPECTIVES

Biologics are redefining the landscape of cardiovascular therapeutics, offering targeted, disease-modifying treatments that address previously "undruggable" mechanisms. Protein, gene, and cell biologics each present distinct advantages, enabling precise intervention in complex cardiovascular processes such as cardiac remodeling, fibrosis, and lipid metabolism. While recent breakthroughs have demonstrated the clinical potential of biologics, several critical challenges must be addressed before their full therapeutic potential can be realized.

One of the most pressing challenges is the efficient delivery of biologics to cardiac tissues.[454,455] Unlike liver or tumor tissues, the

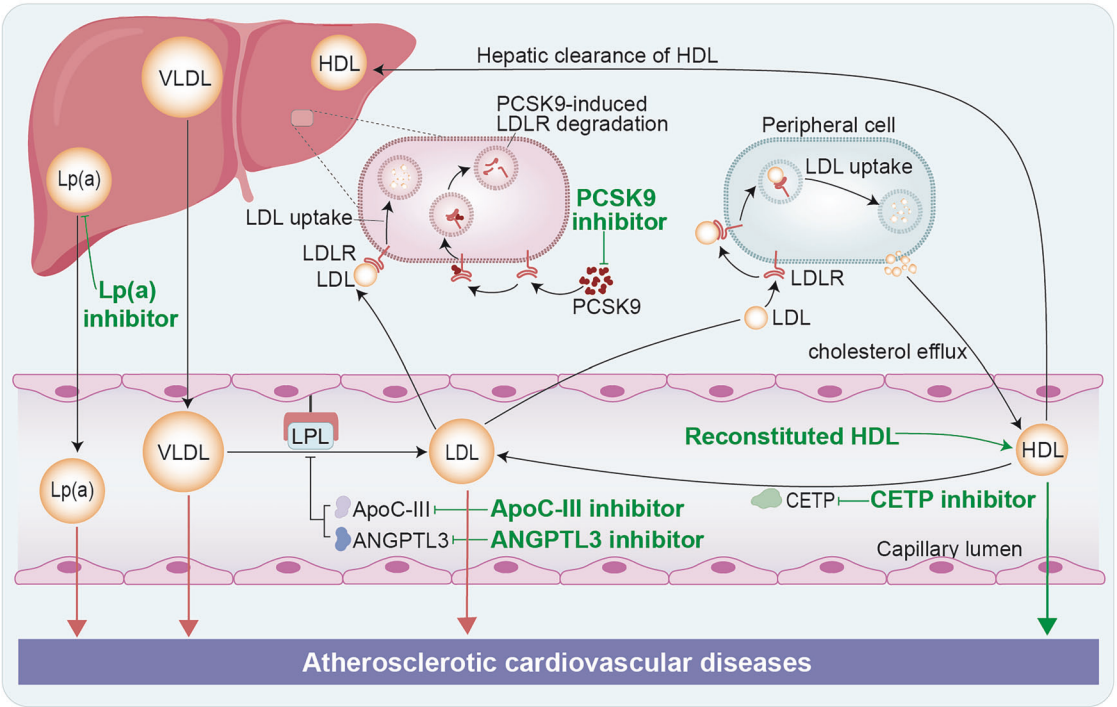

Fig. 6 Emerging mechanisms of lipid metabolism modulation. PCSK9 inhibitors operate by increasing the number of low-density lipoprotein receptors in hepatocytes. ANGPTL3 and apoC3 inhibitors increase triglyceride hydrolysis by preserving lipoprotein lipase activity. CETP inhibitors increase plasma HDL-C levels by preventing cholesterol transfer from HDL to other lipoproteins. A therapeutically induced increase in HDL cholesterol enhances reverse cholesterol transport to the liver, which may reduce the risk of atherosclerotic cardiovascular diseases. Inhibiting the expression of the LPA gene to control serum Lp(a) levels can reduce its proatherogenic effects. PCSK9 proprotein convertase subtilisin/kexin type 9, ANGPTL3 Angiopoietin-like 3, ApoC3 apolipoprotein C3, Lp(a) lipoprotein(a), CETP cholesteryl ester transfer protein, VLDL very low-density lipoprotein, LDL low-density lipoprotein, LDLR low-density lipoprotein receptor, HDL high-density lipoprotein, LPL lipoprotein lipase (Created with BioRender.com)

dense extracellular matrix and dynamic contraction of the heart create significant physical barriers, limiting the distribution of RNA, protein, and cell therapies. Advances in LNPs and responsive nanocarriers offer promising strategies to increase delivery precision. Another challenge is the stability and immunogenicity of biologics,[456] particularly RNA and protein therapeutics. Biologics are susceptible to degradation, aggregation, or immunogenic responses, which complicates storage, transport, and long-term efficacy. Addressing this issue requires innovations in protein engineering and the development of "immune cloaking" technologies to reduce immune detection. Production scalability also remains a major bottleneck, especially for cell therapies such as CAR-T cells, which require patient-specific manufacturing. Automated production systems and allogeneic "off-the-shelf" CAR-T-cell therapies are being explored to streamline the production process.[29] Finally, the long-term safety and efficacy of gene-editing technologies such as CRISPR-Cas9 are still under investigation.[457,458] The potential for off-target effects and long-term genetic changes must be carefully monitored in ongoing clinical trials to ensure patient safety.

Despite these challenges, biologics offer unprecedented opportunities for advancing cardiovascular treatment. Innovations in delivery systems,[459,460] such as myocardium-targeted LNPs and intelligent, responsive nanocarriers, promise to improve cardiac-specific delivery of RNA and protein therapies. The development of immune cloaking technologies and protein engineering could reduce immune responses and improve the stability of biologics, allowing for longer shelf-life and simplified storage conditions.[461,462] Advances in automated cell manufacturing platforms and the shift from patient-specific CAR-T cells to "off-the-shelf" universal CAR-T cells are needed to reduce production time and cost,[462,463] making these therapies more accessible. Additionally, CRISPR-based gene therapies offer the potential for one-time curative treatments for hereditary cardiovascular diseases such as ATTR-CM,[398,463] shifting treatment paradigms from chronic management to permanent correction.

In the future, cross-disciplinary collaboration will be essential to address these challenges and seize emerging opportunities. The integration of artificial intelligence into drug discovery, the optimization of delivery technologies, and automated biomanufacturing could accelerate the development of biologics for CVD treatment.[464–466] The next decade is likely to witness a shift toward personalized and precision-based cardiovascular treatments. By overcoming current limitations, biologics could usher in a new era of cardiovascular care, offering safer, more effective, and personalized treatment options for patients worldwide.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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