

Emerging Therapies for Heart Failure: A Review of Novel Pharmacological Agents, Device-Based Therapies, and Gene Therapy Approaches

¹Okwah, Micah Nnabuko, ²Akinrele, Olaitan Rashidat, ³Moses Adondua Abah, ⁴Micheal Oladosu Abimbola, ⁵Raheemat Oyiza Muhammad, and ⁶Onuoha Nneji Nmecha

¹Department of Chronic Disease Epidemiology, Yale University, Connecticut, United States

²Department of Clinical Sciences, Obafemi Awolowo University, Ile-ife, Osun state, Nigeria

³Department of Biochemistry, Faculty of Biosciences, Federal University Wukari, Wukari, Taraba State, Nigeria

⁴Department of Chemical Sciences, Faculty of Science, Anchor University, Ayobo, Lagos State, Nigeria

⁵Department of Plant Biology, Faculty of Life Sciences, Bayero University Kano, Kano State, Nigeria.

⁶Department of Preventive and Social Medicine, Faculty of clinical sciences, University of Portharcourt, Choba, Rivers State, Nigeria

Abstract

Heart failure (HF) remains a major global public health challenge associated with high morbidity, mortality, recurrent hospitalization, and escalating healthcare costs despite significant advances in conventional treatment strategies. The growing limitations of standard pharmacological and supportive therapies have accelerated the development of innovative therapeutic approaches aimed at improving cardiac function, reducing disease progression, and enhancing patient quality of life. This review examines emerging therapies for heart failure, with emphasis on novel pharmacological agents, device-based interventions, and gene therapy strategies. Recent pharmacological advancements, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, angiotensin receptor-neprilysin inhibitors (ARNIs), soluble guanylate cyclase stimulators, and cardiac myosin activators, have demonstrated substantial clinical benefits in reducing cardiovascular mortality and hospitalization rates. In parallel, device-based therapies such as cardiac resynchronization therapy, implantable cardioverter defibrillators, left ventricular assist devices, and remote monitoring technologies continue to transform the management of advanced HF through improved hemodynamic support and early disease surveillance. Furthermore, gene therapy and regenerative approaches, including SERCA2a gene transfer, CRISPR-mediated genome editing, and stem cell-based cardiac repair, represent promising frontiers targeting the molecular and genetic basis of HF. However, challenges related to long-term safety, clinical efficacy, accessibility, cost, and ethical considerations remain significant barriers to widespread implementation. The review highlights the potential of integrating pharmacological innovation, precision medicine, and advanced biotechnology to redefine future HF management and improve long-term cardiovascular outcomes.

Keywords: Heart failure, Emerging therapies, SGLT2 inhibitors, Device-based therapy, Gene therapy, and Precision medicine

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by structural or functional impairment of ventricular filling or ejection of blood, resulting in inadequate tissue perfusion and systemic congestion. It remains one of the leading causes of cardiovascular morbidity and mortality worldwide, with increasing prevalence attributed to aging populations and the rising burden of hypertension, diabetes mellitus, obesity, and

ischemic heart disease (Heidenreich and Sandhu, 2024). Despite major improvements in cardiovascular care, HF continues to impose substantial economic and healthcare challenges due to frequent hospitalization, disease progression, and reduced quality of life (Lam *et al.*, 2023).

Corresponding Author: Moses Adondua Abah

Department of Biochemistry, Faculty of
Biosciences, Federal University Wukari,

The clinical heterogeneity of HF, particularly heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), further complicates disease management and therapeutic outcomes (Masarone *et al.*, 2024). Consequently, there is increasing emphasis on the development of innovative therapeutic strategies capable of addressing the multifactorial mechanisms underlying HF progression (Bismpos *et al.*, 2024).

The pathophysiology of HF involves intricate interactions among neurohormonal activation, myocardial remodeling, oxidative stress, inflammation, endothelial dysfunction, and metabolic abnormalities. Persistent activation of the renin-angiotensin-aldosterone system and sympathetic nervous system contributes significantly to ventricular hypertrophy, fibrosis, and progressive decline in cardiac function (Chan and Siddiqui, 2024). Conventional therapies such as beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and diuretics have improved survival and symptom control; however, residual cardiovascular risk remains substantial in many patients (Heidenreich and Sandhu, 2024). Advances in translational and molecular cardiology have therefore stimulated interest in therapies targeting cellular metabolism, inflammation, and myocardial contractility to achieve improved clinical outcomes (Masarone *et al.*, 2024). These scientific developments have accelerated the transition from symptom-based management toward precision-oriented and mechanism-driven therapeutic approaches in HF care (Lam *et al.*, 2023).

Recent pharmacological innovations have significantly transformed the contemporary management of HF. Among these, sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as major therapeutic breakthroughs due to their cardioprotective effects extending beyond glycemic regulation (Chen *et al.*, 2024). Clinical evidence demonstrates that SGLT2 inhibitors reduce cardiovascular mortality, improve cardiac function, and decrease HF-related hospitalization in both diabetic and non-diabetic populations (Vellio *et al.*, 2023). Mechanistically, these agents improve myocardial energetics, reduce oxidative stress, and enhance renal-cardiovascular interactions (Xie *et al.*, 2023). In addition, angiotensin receptor-neprilysin inhibitors (ARNIs) have shown superior efficacy compared with traditional renin-angiotensin system inhibitors through enhanced natriuretic peptide activity and attenuation of adverse cardiac remodeling (Das, 2024). Current evidence further supports the combined therapeutic potential of SGLT2 inhibitors and ARNIs in optimizing cardiac performance and improving long-term prognosis among HF patients (Ezhumalai *et al.*, 2024).

Beyond pharmacological interventions, device-based therapies and emerging genetic approaches are reshaping the management of advanced HF. Technologies such as cardiac resynchronization therapy, implantable cardioverter defibrillators, and left ventricular assist devices have demonstrated significant benefits in improving survival and functional capacity in selected patient populations (Masarone *et al.*, 2024). Furthermore, digital health technologies, remote monitoring systems, and wearable sensors are enhancing early detection of decompensation and facilitating individualized patient management (Heidenreich and Sandhu, 2024). Recent advances in gene therapy and regenerative medicine also present promising opportunities for targeting the molecular basis of HF through myocardial repair and restoration of impaired calcium handling pathways (Bismpos *et al.*, 2024). Although these therapies remain associated with challenges related to safety, accessibility, cost, and long-term efficacy, they represent important advancements toward personalized cardiovascular medicine and next-generation HF treatment strategies (Chan and Siddiqui, 2024).

This review critically examines emerging therapies for heart failure with particular emphasis on novel pharmacological agents, device-based interventions, and gene therapy approaches. The review explores the evolving understanding of heart failure pathophysiology and highlights how recent therapeutic innovations are improving disease management and patient outcomes. Special attention is given to the clinical relevance of sodium-glucose cotransporter-2 inhibitors, angiotensin receptor-neprilysin inhibitors, soluble guanylate cyclase stimulators, and cardiac myosin activators in modern HF treatment. In addition, the review evaluates the role of advanced device-based therapies such as cardiac resynchronization therapy, implantable cardioverter defibrillators, left ventricular assist devices, and digital monitoring technologies in reducing mortality and hospitalization rates. The review also discusses recent progress in gene therapy, regenerative medicine, and precision-based cardiovascular interventions aimed at addressing the molecular and genetic mechanisms of HF. Furthermore, major challenges associated with the implementation of these emerging therapies, including economic limitations, ethical concerns, regulatory barriers, and safety considerations, are examined. Finally, the review provides insight into future perspectives in heart failure management, including personalized medicine, artificial intelligence integration, and combined therapeutic strategies that may redefine the future landscape of cardiovascular care.

PATHOPHYSIOLOGY OF HEART FAILURE

Heart failure (HF) is a progressive cardiovascular syndrome caused by structural and functional abnormalities that impair ventricular filling and cardiac output. Its pathophysiology involves interconnected hemodynamic, neurohormonal, inflammatory, metabolic, and molecular mechanisms that progressively reduce myocardial efficiency and worsen cardiac performance (Ranek *et al.*, 2022; Heidenreich and Sandhu, 2024). Beyond impaired pumping ability, HF is strongly associated with neurohormonal activation, myocardial remodeling, oxidative stress, fibrosis, mitochondrial dysfunction, and genetic abnormalities, all of which contribute to disease progression and increased cardiovascular mortality (Lam *et al.*, 2023). Improved understanding of these mechanisms has supported the development of therapies that target disease progression rather than symptom control alone (Braunwald, 2024; Masarone *et al.*, 2024).

NEUROHORMONAL DYSREGULATION

Reduced cardiac output activates compensatory neurohormonal systems, particularly the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), to maintain systemic perfusion (Chan and Siddiqui, 2024). Persistent SNS activation increases catecholamine release, causing tachycardia, vasoconstriction, increased myocardial oxygen demand, and cardiomyocyte apoptosis (Bismpos *et al.*, 2024). Chronic RAAS activation promotes sodium and water retention, ventricular hypertrophy, endothelial dysfunction, and myocardial fibrosis through angiotensin II and aldosterone activity (Heidenreich and Sandhu, 2024). Although initially compensatory, prolonged activation becomes maladaptive and accelerates HF progression (McDonagh *et al.*, 2023). Impaired natriuretic peptide signaling further contributes to disease progression due to increased neprilysin-mediated degradation and receptor desensitization (Das, 2024). This understanding led to the development of angiotensin receptor-neprilysin inhibitors (ARNIs), which enhance natriuretic peptide activity while suppressing RAAS activation (Ezhumalai *et al.*, 2024).

CARDIAC REMODELING AND FIBROSIS

Cardiac remodeling involves structural and functional myocardial changes caused by chronic hemodynamic stress, ischemia, and neurohormonal activation. These changes include ventricular dilation, cardiomyocyte hypertrophy, extracellular matrix reorganization, and impaired systolic and diastolic function (Masarone *et al.*, 2024). Initially adaptive, persistent remodeling eventually becomes maladaptive, worsening ventricular dysfunction

and increasing mortality risk (Braunwald, 2024). Myocardial fibrosis, characterized by excessive collagen and extracellular matrix deposition, is a major feature of pathological remodeling. Fibrotic pathways involving transforming growth factor-beta (TGF- β), angiotensin II, and aldosterone stimulate fibroblast activation and tissue stiffening (Lam *et al.*, 2023). Fibrosis impairs ventricular relaxation and electrical conduction, contributing to mechanical dysfunction and arrhythmias (Harrington and Moore-Morris, 2024; Lunde *et al.*, 2024). Inflammatory and immunometabolic processes also promote fibrogenesis (Hoque *et al.*, 2024). Emerging therapies such as SGLT2 inhibitors and ARNIs may reduce fibrosis and partially reverse adverse remodeling (Chen *et al.*, 2024).

INFLAMMATION, OXIDATIVE STRESS, AND MITOCHONDRIAL DYSFUNCTION

Inflammation and oxidative stress significantly contribute to HF progression. Elevated inflammatory cytokines such as TNF- α , IL-1, and IL-6 promote myocardial injury, fibrosis, endothelial dysfunction, and ventricular remodeling (Masarone *et al.*, 2024). Chronic inflammation also disrupts calcium handling and myocardial contractility (Van Linthout and Tschöpe, 2017). Oxidative stress results from excessive reactive oxygen species (ROS) overwhelming antioxidant defenses. ROS damage mitochondrial DNA, proteins, lipids, and ion channels, impairing cardiomyocyte function (Chan and Siddiqui, 2024). Mitochondrial dysfunction further reduces ATP production and myocardial energy efficiency through impaired oxidative phosphorylation and calcium overload (Xie *et al.*, 2023). SGLT2 inhibitors may improve mitochondrial bioenergetics and reduce oxidative stress, contributing to better cardiovascular outcomes (Velliou *et al.*, 2023; Abah *et al.*, 2025).

GENETIC AND MOLECULAR MECHANISMS

Genetic and molecular abnormalities contribute significantly to HF, especially in inherited cardiomyopathies. Mutations affecting sarcomeric proteins, ion channels, cytoskeletal structures, and mitochondrial genes impair myocardial contractility and electrical conduction (Masarone *et al.*, 2024). Genetic susceptibility also influences remodeling, arrhythmogenesis, and progression to advanced HF (McDonagh *et al.*, 2021). Abnormal intracellular calcium regulation, particularly impaired SERCA2a activity, disrupts myocardial contraction and relaxation (Heidenreich & Sandhu, 2024). Altered mitochondrial metabolic pathways further worsen energetic deficits and contractile dysfunction. Advances in molecular cardiology have stimulated interest in gene

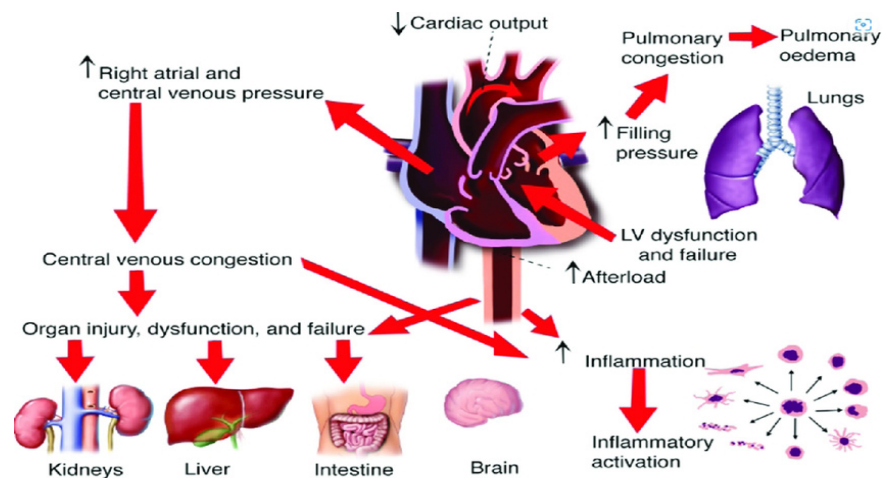


Fig1. Pathophysiology of heart failure. It shows the major mechanisms involved in heart failure progression, including inflammation, oxidative stress, mitochondrial dysfunction, and cardiac remodeling. These interconnected processes impair cardiac function, reduce cardiac output, and worsen ventricular dysfunction

Sources: Ranek *et al.* (2022); Abah *et al.* (2025)

therapy, regenerative medicine, and genome-editing technologies such as CRISPR/Cas9 for targeted HF management (Harrington and Moore-Morris, 2024; Hoque *et al.*, 2024).

NOVEL PHARMACOLOGICAL AGENTS

Recent advances in heart failure (HF) pharmacotherapy have significantly transformed the management of both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Contemporary therapeutic strategies increasingly target the molecular and metabolic mechanisms underlying HF

progression rather than focusing solely on symptomatic relief (Bozkurt, 2024). Novel agents including sodium-glucose cotransporter-2 (SGLT2) inhibitors, angiotensin receptor-neprilysin inhibitors (ARNIs), soluble guanylate cyclase (sGC) stimulators, and cardiac myosin activators have demonstrated substantial benefits in reducing cardiovascular mortality, improving ventricular function, and lowering hospitalization risk (Maddox *et al.*, 2021; Lima *et al.* 2025; Vaduganathan *et al.*, 2026). These therapeutic innovations represent a major paradigm shift toward precision-based and mechanism-directed HF management.

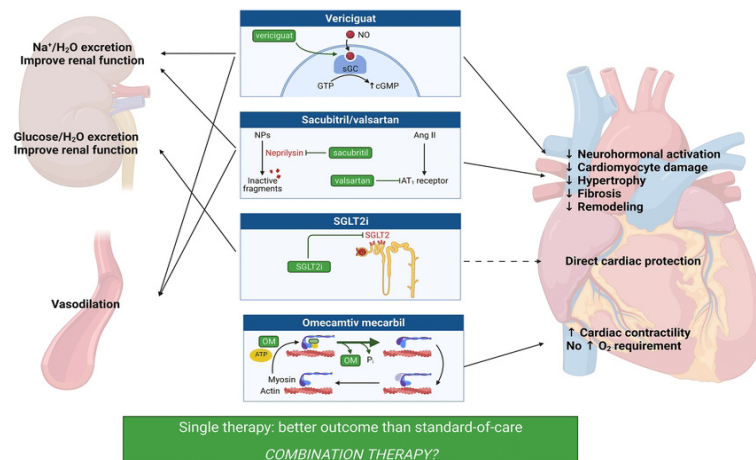


Fig2. Novel pharmacotherapies for heart failure, their mechanisms of action and final effects. This figure illustrates novel pharmacological therapies used in heart failure management and their mechanisms of action. These agents improve cardiac function by reducing fluid overload, enhancing myocardial efficiency, decreasing ventricular remodeling, and improving cardiac contractility, ultimately leading to better clinical outcomes and reduced mortality.

Source: Aimo *et al.* (2022)

SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as foundational therapies in modern HF management because of their broad cardioprotective and renoprotective effects. These agents reduce sodium and glucose reabsorption within the proximal renal tubules, thereby promoting natriuresis, osmotic diuresis, and reduction of cardiac preload and afterload (Xie *et al.*, 2023). Beyond their renal actions, SGLT2 inhibitors improve myocardial energetics, reduce oxidative stress, attenuate inflammation, and enhance mitochondrial efficiency (Abah *et al.*, 2025). Clinical evidence from DAPA-HF and DELIVER has demonstrated significant reductions in cardiovascular death and HF hospitalization across the ejection fraction spectrum, including severe HF phenotypes (Inciardi *et al.*, 2025). Furthermore, early initiation of SGLT2 inhibitors appears particularly beneficial in high-risk patients with worsening HF and concomitant renal dysfunction (Severino *et al.*, 2023). Their favorable safety profile and multidimensional cardiovascular benefits have consequently established SGLT2 inhibitors as central components of guideline-directed HF therapy (Ezhumalai *et al.*, 2024).

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS (ARNIs)

Angiotensin receptor-neprilysin inhibitors (ARNIs) provide dual neurohormonal modulation through simultaneous inhibition of neprilysin and blockade of the renin-angiotensin-aldosterone system (RAAS). Sacubitril/valsartan enhances endogenous natriuretic peptide activity while suppressing the harmful cardiovascular

effects of angiotensin II, thereby promoting vasodilation, natriuresis, and attenuation of myocardial fibrosis and ventricular remodeling (Greenberg, 2020). In addition to regulating natriuretic peptides, neprilysin inhibition also influences several vasoactive and inflammatory substrates involved in cardiovascular homeostasis (D'Elia *et al.*, 2017). Clinical studies have demonstrated that sacubitril/valsartan significantly reduces cardiovascular mortality and HF hospitalization compared with conventional RAAS inhibitors, particularly among patients with HFrEF (Ezhumalai *et al.*, 2024). ARNIs have also demonstrated superior effects on ventricular remodeling, symptom improvement, and quality of life, thereby establishing their role as cornerstone therapies in contemporary HF management.

SOLUBLE GUANYLATE CYCLASE (sGC) STIMULATORS

Endothelial dysfunction and impaired nitric oxide signaling contribute significantly to HF progression through reduced cyclic guanosine monophosphate (cGMP) activity and vascular dysregulation. Soluble guanylate cyclase (sGC) stimulators target this pathway by directly stimulating sGC and enhancing intracellular cGMP production independently of nitric oxide availability (Kansakar *et al.*, 2021). Vericiguat, the first clinically approved sGC stimulator for HF, improves endothelial function, vascular relaxation, and myocardial compliance while attenuating ventricular remodeling. Clinical evidence indicates that vericiguat reduces the risk of recurrent HF hospitalization and cardiovascular events in patients with worsening chronic HFrEF despite guideline-directed therapy (Aimo *et al.*, 2022).

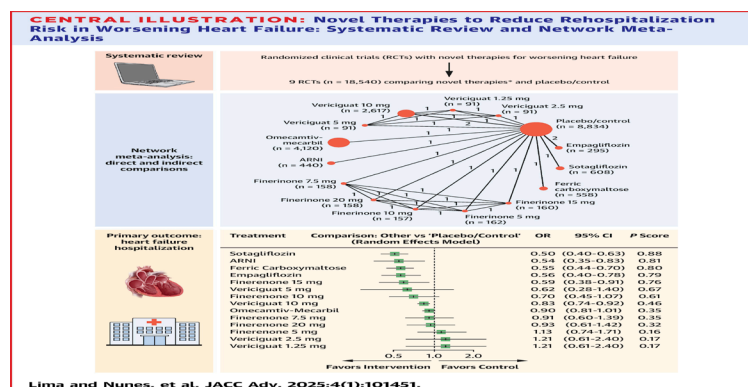


Fig3. Novel pharmacotherapies to reduce the risk of rehospitalization in patients with worsening heart failure. The figure depicts that administration of sodium-glucose co-transporter 2 (SGLT2) inhibitors, angiotensin receptor-neprilysin inhibitors (ARNI), and ferric carboxymaltose significantly reduces rehospitalization rates for patients with worsening heart failure

Source: Lima *et al.* (2025)

Recent meta-analytic evidence further supports the role of vericiguat and related therapies in lowering rehospitalization risk among patients with worsening HF syndromes (Lima *et al.*, 2025). Although the overall mortality benefit remains modest, sGC stimulators provide an important therapeutic option for high-risk HF patients with persistent symptomatic disease.

CARDIAC MYOSIN ACTIVATORS

Cardiac myosin activators represent a novel therapeutic strategy aimed at directly improving myocardial contractility without increasing intracellular calcium concentrations or myocardial oxygen demand. Omecamtiv mecarbil selectively enhances the interaction between actin and myosin filaments, thereby prolonging systolic ejection time and improving stroke volume (Teerlink *et al.*, 2021).

Unlike traditional inotropic agents, cardiac myosin activators improve cardiac performance with lower risks of arrhythmogenesis and excessive myocardial energy consumption. The GALACTIC-HF trial demonstrated that omecamtiv mecarbil modestly reduced HF events and cardiovascular complications among patients with chronic

HFREF, particularly those with severely reduced ejection fraction (Teerlink *et al.*, 2021). Nevertheless, uncertainty regarding long-term mortality benefit and patient selection continues to limit widespread clinical adoption. Additional studies are therefore required to clarify the therapeutic positioning of cardiac myosin activators within multidrug HF treatment strategies.

DEVICE-BASED THERAPIES

Device-based therapies remain fundamental in the management of patients with moderate-to-advanced heart failure (HF), particularly those with persistent symptoms, ventricular dyssynchrony, malignant arrhythmias, or refractory circulatory failure despite optimal medical therapy. Contemporary HF management increasingly integrates implantable devices, mechanical circulatory support systems, and digital monitoring technologies to improve survival, reduce hospitalization, and enhance quality of life (Bozkurt, 2024; Heidenreich and Sandhu, 2024). Advances in cardiac electrophysiology, hemodynamic monitoring, and artificial intelligence (AI) have further strengthened the role of device-based interventions in precision HF care.

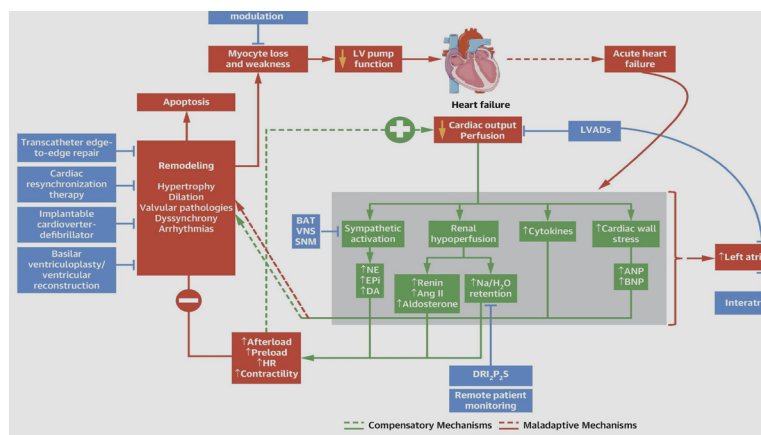


Fig4.How various medical devices target specific malfunctioning pathways in heart failure pathophysiology. The red boxes highlight processes such as ventricular remodeling, hypertrophy, and apoptosis that worsen heart failure. Blue boxes indicate therapeutic interventions like implantable cardioverter-defibrillators, cardiac resynchronization therapy, and Left Ventricular Assist Devices (LVADs) designed to counteract these pathways

Source: Husam *et al.* (2023)

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

Cardiac resynchronization therapy (CRT) is an established intervention for patients with heart failure with reduced ejection fraction (HFREF) and ventricular conduction abnormalities, particularly left bundle branch block (LBBB). CRT improves ventricular synchrony through coordinated biventricular pacing, thereby enhancing

cardiac output and reversing adverse ventricular remodeling (Mullens *et al.*, 2021). Current guidelines recommend CRT in symptomatic patients with reduced ejection fraction, prolonged QRS duration, and persistent symptoms despite guideline-directed medical therapy (McDonagh *et al.*, 2021). Clinical evidence demonstrates that CRT significantly reduces HF hospitalization, improves functional capacity, and lowers cardiovascular mortality

in appropriately selected patients (Maddox *et al.*, 2021). Nevertheless, a subset of patients remains non-responsive to conventional CRT, prompting increasing interest in conduction system pacing approaches such as His-bundle pacing and left bundle branch area pacing. These emerging pacing modalities may improve electrical synchrony and optimize CRT response while reducing pacing-related complications (Cano *et al.*, 2023).

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDs)

Implantable cardioverter defibrillators (ICDs) are essential in the prevention of sudden cardiac death (SCD) among high-risk HF patients. ICDs continuously monitor cardiac rhythm and deliver anti-tachycardia pacing or electrical defibrillation to terminate life-threatening ventricular arrhythmias (Al-Khatib *et al.*, 2018). Their greatest clinical benefit is observed in patients with significantly reduced left ventricular ejection fraction and elevated arrhythmic risk despite optimized medical therapy. Although ICD therapy substantially reduces SCD incidence, contemporary evidence suggests that more refined patient selection criteria may be required because improvements in pharmacological therapy have altered arrhythmic risk profiles in chronic HF populations (Deckers *et al.*, 2021). Appropriate risk stratification therefore remains essential to maximize therapeutic benefit while minimizing unnecessary device implantation and associated complications such as inappropriate shocks, infection, and lead malfunction.

LEFT VENTRICULAR ASSIST DEVICES (LVADs)

Left ventricular assist devices (LVADs) are mechanical circulatory support systems utilized in patients with advanced or end-stage HF who remain symptomatic despite maximal therapy. LVADs provide continuous circulatory

support by unloading the failing left ventricle and improving systemic perfusion (Estep *et al.*, 2015). These devices are used both as bridge-to-transplant therapy and as destination therapy in patients who are not eligible for heart transplantation. Technological advancements in fully magnetically levitated continuous-flow devices have significantly improved long-term outcomes and device durability. The MOMENTUM 3 trial demonstrated superior five-year survival and lower rates of pump thrombosis and stroke with fully magnetically levitated LVADs compared with older axial-flow systems (Mehra *et al.*, 2022). Despite these advances, LVAD-associated complications including bleeding, infection, thromboembolism, and right ventricular failure continue to limit long-term outcomes (Kirklin *et al.*, 2017). Ongoing innovations therefore focus on improving biocompatibility, reducing adverse events, and enhancing patient quality of life.

REMOTE MONITORING AND WEARABLE TECHNOLOGIES

Remote monitoring technologies have emerged as important tools for reducing HF hospitalization and improving long-term disease management. Telemonitoring systems enable continuous assessment of hemodynamic and physiological parameters, facilitating early identification of clinical deterioration and timely therapeutic intervention. The CHAMPION trial demonstrated that wireless pulmonary artery pressure monitoring significantly reduced HF-related hospitalization in chronic HF patients (Abraham *et al.*, 2011). Similarly, real-world evidence has confirmed the effectiveness of ambulatory hemodynamic monitoring in improving outpatient HF management and reducing recurrent admissions (Desai *et al.*, 2017). Recent advances in wearable sensors and AI-assisted management systems are further transforming HF care through predictive analytics and individualized risk stratification. Machine

Table 1. Overview of major device-based therapies and their clinical applications in heart failure management

Device-Based Therapy	Primary mechanism	Clinical benefit	Limitations/Considerations
Cardiac Resynchronization Therapy (CRT)	Biventricular pacing restores ventricular synchrony in patients with conduction abnormalities	Improves cardiac output, reverses ventricular remodeling, reduces hospitalization and mortality	Best outcomes in patients with LBBB and prolonged QRS duration; non-response may occur
Implantable Cardioverter Defibrillators (ICDs)	Detects and terminates life-threatening ventricular arrhythmias through pacing or defibrillation	Prevents sudden cardiac death and improves survival in high-risk HFrEF patients	Risk of inappropriate shocks, infection, lead malfunction, and psychological distress

Left Ventricular Assist Devices (LVADs)	Mechanical circulatory support unloads the failing left ventricle and maintains systemic perfusion	Serves as bridge-to-transplant or destination therapy; improves survival and functional capacity	Complications include thrombosis, bleeding, stroke, infection, and right ventricular failure
Remote Monitoring and Wearable Technologies	Continuous monitoring of physiological and hemodynamic parameters using sensors and AI-assisted systems	Enables early detection of decompensation, reduces rehospitalization, and supports personalized management	Requires patient adherence, digital infrastructure, and data integration for optimal effectiveness

learning algorithms can integrate physiological, behavioral, and device-derived data to predict HF decompensation and optimize treatment decisions (Yoon *et al.*, 2023). In addition, continuous telemedical management integrated with cardiac implantable electronic devices has demonstrated promising benefits in reducing healthcare utilization and improving clinical outcomes (Veres *et al.*, 2025). Collectively, these digital innovations represent a major advancement toward precision-based and proactive HF management.

GENE THERAPY APPROACHES

Gene therapy has emerged as a promising strategy for the management of heart failure (HF) by targeting the molecular abnormalities responsible for impaired myocardial function and progressive ventricular remodeling. Unlike conventional pharmacological therapies that mainly control symptoms and neurohormonal activation, gene-based therapies aim to correct defective cellular pathways and restore myocardial performance at the molecular level (Ylä-Herttua and Baker, 2017). Advances in molecular cardiology and regenerative medicine have consequently accelerated interest in precision-based therapeutic approaches for both inherited and acquired forms of HF.

SERCA2A GENE THERAPY

One of the most extensively investigated approaches in cardiac gene therapy targets sarcoplasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a), a critical regulator of intracellular calcium cycling and myocardial contractility. Reduced SERCA2a activity contributes significantly to impaired calcium handling and systolic dysfunction in HF. SERCA2a gene transfer aims to restore calcium homeostasis, improve myocardial relaxation, and enhance ventricular performance (Naim *et al.*, 2013). Initial clinical studies reported improvements in ventricular function and symptomatic status following SERCA2a gene delivery. However, larger clinical trials later produced less favorable outcomes, largely because of challenges associated with vector uptake and sustained myocardial expression (Hulot

et al., 2016). Despite these limitations, SERCA2a therapy remains an important proof-of-concept for molecularly targeted HF treatment strategies.

CRISPR AND GENOME EDITING STRATEGIES

The development of CRISPR-Cas9 technology has introduced new opportunities for precision genome editing in cardiovascular medicine. CRISPR-based systems enable targeted correction of disease-causing mutations associated with inherited cardiomyopathies and HF with high specificity (Doudna and Charpentier, 2014). Experimental studies have demonstrated the potential of genome editing to modify genes involved in myocardial dysfunction, fibrosis, and arrhythmogenesis (Chadwick and Musunuru, 2017). Despite its transformative potential, CRISPR technology raises important ethical and safety concerns, including off-target mutations, long-term genomic instability, and ethical issues surrounding human genetic modification. Consequently, careful regulatory oversight and further translational studies remain essential before widespread clinical application in HF management.

STEM CELL AND REGENERATIVE GENE-BASED THERAPIES

Stem cell and regenerative gene-based therapies aim to repair damaged myocardium and stimulate cardiac regeneration in patients with advanced HF. Mesenchymal stem cells, cardiac progenitor cells, and induced pluripotent stem cells have been investigated for their potential to promote angiogenesis, reduce fibrosis, and improve myocardial repair through paracrine signaling mechanisms (Menasché and Vaneaux, 2016). Regenerative therapies may also be combined with gene transfer approaches to enhance cell survival, differentiation, and myocardial integration. Although early clinical studies have demonstrated modest improvements in ventricular function and functional capacity, inconsistent therapeutic efficacy and limited long-term engraftment remain major challenges (Kir *et al.*, 2021). Additional concerns include

immune rejection, arrhythmogenic risk, and variability in stem cell preparation protocols. Nevertheless, ongoing advances in regenerative medicine continue to strengthen the future potential of gene-based cardiac repair strategies in HF treatment.

Table 2. *Gene therapy and regenerative approaches in heart failure*

Approach	Target/mechanism	Clinical data	Limitation	Reference
Gene Therapy (AAV1-SERCA2a)	Enhances calcium handling	CUPID I/II trials	CUPID I positive; CUPID II neutral	Greenberg <i>et al.</i> , 2016
Stem Cell Therapy (MSCs, CPCs, iPSCs)	Paracrine signaling, repair, angiogenesis	Mixed clinical trial outcomes	Heterogeneity in delivery, survival of cells	Bolli <i>et al.</i> , 2011
microRNA/siRNA therapies	microRNA / siRNA therapies	Preclinical	Delivery and off-target effects remain concerns	Gabisonia <i>et al.</i> , 2019
CRISPR-based editing	Correct inherited cardiomyopathy mutations	Preclinical	Safety, ethical/regulatory barriers	Musunuru <i>et al.</i> , 2018

CHALLENGES AND LIMITATIONS

Despite major advances in pharmacological, device-based, and gene-directed therapies for heart failure (HF), several challenges continue to limit their widespread clinical implementation. Safety concerns remain particularly important with emerging therapies, especially gene editing and regenerative approaches, where risks such as immune reactions, arrhythmias, off-target genetic modifications, and long-term adverse effects require careful evaluation (Doudna and Charpentier, 2014). Device-based interventions including implantable cardioverter defibrillators and left ventricular assist devices are also associated with complications such as infection, thrombosis, bleeding, and device malfunction, which may negatively affect long-term outcomes (Kirklin *et al.*, 2017).

Cost and accessibility represent additional barriers, particularly in low- and middle-income countries where advanced HF therapies remain largely unavailable because of high procedural costs, limited healthcare infrastructure, and inadequate specialist availability (Heidenreich and Sandhu, 2024). The financial burden associated with long-term pharmacotherapy, implantable devices, and personalized gene-based treatments further contributes to disparities in healthcare access and treatment adherence. Regulatory and ethical concerns also continue to influence the development and application of innovative HF therapies. Genome editing technologies such as CRISPR-Cas9 raise ethical questions regarding genetic modification, long-term genomic safety, and equitable access to precision medicine (Chadwick and Musunuru, 2017). In addition, translational barriers including limited large-scale clinical trials, heterogeneity in patient populations, difficulties in vector delivery, and inconsistent long-term efficacy continue to slow the transition of experimental therapies

from laboratory research to routine clinical practice (Hulot *et al.*, 2016).

FUTURE PERSPECTIVES

The future of heart failure (HF) management is increasingly centered on personalized and precision medicine approaches that integrate genetic, molecular, clinical, and biomarker data to optimize therapeutic decision-making. Advances in genomics, transcriptomics, and artificial intelligence (AI)-driven analytics are expected to improve patient stratification, identify novel therapeutic targets, and enhance prediction of treatment response across diverse HF phenotypes (Bozkurt, 2024). Precision-based care may therefore enable more individualized interventions while minimizing adverse effects and therapeutic inefficiency. Combination therapeutic strategies are also expected to play a major role in future HF management. Contemporary evidence supports the use of multidrug regimens combining sodium-glucose cotransporter-2 (SGLT2) inhibitors, angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, and mineralocorticoid receptor antagonists to achieve synergistic cardioprotective effects and improve long-term survival (Vaduganathan *et al.*, 2026). Future therapeutic models will likely integrate pharmacological agents with device-based interventions and molecular therapies to provide comprehensive and mechanism-directed treatment for both HFrEF and HFpEF populations.

Artificial intelligence and digital technologies are further transforming HF care through predictive analytics, remote monitoring, and automated clinical decision support systems. Machine learning algorithms can analyze large volumes of physiological and clinical data to detect early signs of decompensation, predict hospitalization risk, and guide individualized treatment adjustments (Yoon *et al.*, 2023). Integration of wearable sensors, telemonitoring platforms, and AI-assisted diagnostics is therefore

expected to strengthen proactive and patient-centered HF management. Regenerative cardiology also represents a promising frontier in HF therapy. Advances in stem cell therapy, tissue engineering, and gene editing technologies may eventually enable restoration of damaged myocardium and reversal of ventricular dysfunction (Kir *et al.*, 2021). Although important scientific and translational challenges remain, continued progress in regenerative medicine may ultimately shift HF treatment from symptomatic management toward true myocardial repair and functional recovery.

CONCLUSION

Heart failure remains a major global cardiovascular challenge associated with substantial morbidity, mortality, and healthcare burden despite significant advances in conventional treatment strategies. Recent developments in pharmacological therapies, device-based interventions, and gene-directed approaches have considerably transformed the therapeutic landscape of heart failure management. Novel agents such as sodium-glucose cotransporter-2 inhibitors, angiotensin receptor-neprilysin inhibitors, soluble guanylate cyclase stimulators, and cardiac myosin activators have demonstrated important clinical benefits in improving cardiac function, reducing hospitalization, and enhancing survival outcomes across different heart failure phenotypes. In addition, device-based therapies including cardiac resynchronization therapy, implantable cardioverter defibrillators, left ventricular assist devices, and remote monitoring technologies have strengthened the management of advanced and high-risk heart failure patients through improved hemodynamic support, arrhythmia prevention, and early detection of clinical deterioration.

Emerging gene therapy and regenerative medicine approaches further highlight the growing potential for precision-based and disease-modifying interventions aimed at myocardial repair and restoration of cardiac function. Despite these promising advances, important challenges related to safety, cost, accessibility, ethical concerns, and translational limitations continue to hinder widespread clinical implementation. Future progress in heart failure management will therefore depend on continued multidisciplinary research, integration of artificial intelligence and digital health technologies, optimization of personalized therapeutic strategies, and expansion of regenerative cardiology approaches. Collectively, these innovations have the potential to significantly improve long-term outcomes and redefine the future of heart failure care.

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