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## Emerging therapeutic strategies in heart failure management: A narrative review of current evidence and future directions

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### Abstract

Heart failure (HF) represents a critical, progressively worsening global health issue, impacting millions and stemming from a myriad of etiological factors including ischemic heart disease, hypertension, valvular heart diseases, and various cardiomyopathies. As a syndrome marked by the heart's diminished capacity to pump sufficient blood to meet the body's needs, HF manifests through severe symptoms, recurrent hospitalizations, and elevated mortality rates. Traditional therapeutic strategies have predominantly aimed at symptom mitigation, fluid overload reduction, and improving cardiac output through a regimen of pharmacologic agents such as angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics, supplemented by device-oriented interventions like implantable cardioverter-defibrillators and cardiac resynchronization therapy. Despite these interventions, the inexorable advance of HF poses a relentless challenge, driven by complex processes like neurohormonal activation, cardiac fibrosis, and cellular remodeling. Recent endeavors in the field have been directed towards unveiling innovative therapeutic strategies that confront these foundational mechanisms head-on. Notably, the advent of gene therapy and cutting-edge gene-editing technologies, such as CRISPR-Cas9, shines a light on the possibility of amending genetic aberrations implicated in HF. Moreover, the sphere of regenerative medicine, with its focus on stem cell therapy and tissue engineering, emerges as a beacon of hope for regenerating damaged myocardium and reinstating cardiac function. The push towards precision medicine further exemplifies the shift towards customizing HF treatment based on individual patient characteristics, incorporating genetic, biomarker, and comorbidity profiles. The integration of artificial intelligence and machine learning into HF care is revolutionizing the development of predictive models, risk stratification, and tailored treatment plans. This narrative review delves into the latest breakthroughs in HF therapy, spotlighting their revolutionary potential to transform HF management by addressing the disease's root causes. Through this exploration, our aim is to offer an extensive overview of the changing landscape in HF treatment, inspiring optimism among patients and healthcare professionals for a future with more effective HF management strategies.

**Keywords:** Heart failure, emerging therapies, pharmacological advancements, device-based interventions, regenerative medicine, precision medicine, cardiac rehabilitation, novel treatments for heart failure, heart failure management, cardiac remodelling, therapeutic targets in heart failure, cardiovascular disease, heart failure prevention

### Introduction

Heart failure represents a pressing global health challenge with profound implications for individuals and healthcare systems worldwide. The complex and multifaceted nature of this disease significantly diminishes the quality of life for affected individuals and places a substantial financial burden on healthcare resources<sup>[1]</sup>. This narrative review delves into the critical topic of "Emerging Therapeutic Strategies in Heart Failure Management," focusing on innovative therapies poised to revolutionize the care of heart failure patients. The importance of this review extends beyond evaluating new treatments; it underscores the urgency of addressing heart failure as a major public health concern demanding innovative solutions.

The prevalence of heart failure is escalating globally, affecting approximately 64 million individuals, a number expected to rise given demographic shifts and an increasing prevalence of cardiovascular risk factors like hypertension, diabetes, and obesity<sup>[1]</sup>. The economic impact of heart failure is staggering, with healthcare expenditures associated with this

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condition reaching billions of dollars annually [2]. Beyond financial costs, heart failure profoundly compromises quality of life, manifesting in symptoms such as dyspnea, fatigue, and exercise intolerance, ultimately shortening life expectancy [3].

Therapeutic strategies for heart failure have evolved significantly in recent decades, driven by advances in research and clinical practice. Pharmacological therapies including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin receptor blockers (ARBs), and diuretics remain foundational in managing symptoms and improving cardiac function [4]. Additionally, implantable devices such as implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) have demonstrated substantial reductions in mortality and hospitalizations among select patient populations [5,6]. While cardiac transplantation remains the gold standard for end-stage heart failure, its widespread application is limited by organ availability [7].

Despite notable therapeutic advancements, significant challenges persist. Not all patients respond optimally to current treatments, and disease progression often continues unabated. Treatment complexity is compounded by adverse effects, medication intolerances, and non-adherence to therapy regimens [8]. There is a critical need for novel therapeutic approaches to address these unmet needs.

Emerging therapies encompass a spectrum of innovative strategies, including advanced pharmacological agents, device-based interventions, regenerative medicine initiatives, and precision medicine endeavors. These novel approaches aim to improve patient outcomes, enhance quality of life, and target underlying pathophysiological mechanisms more effectively than conventional therapies.

This narrative review comprehensively evaluates emerging therapies poised to transform heart failure management fundamentally. By analyzing recent advancements in depth, this review contributes to the existing knowledge base on heart failure, fostering innovation and progress in the field. Each emerging therapy is scrutinized for its mechanisms of action, clinical efficacy, and potential advantages over established modalities. Insights gleaned from this review will aid clinicians and researchers in making informed decisions about integrating novel therapies into clinical practice.

This narrative review explores a diverse array of emerging therapeutics for heart failure, offering a comprehensive examination of breakthroughs poised to revolutionize the treatment of this widespread global health challenge. Through identifying areas ripe for further investigation, this review aims to stimulate ongoing innovation and research in heart failure management.

## Review

### Methods

#### Search Strategy

A systematic and comprehensive search strategy was executed to ensure the rigor and inclusivity of this narrative review. PubMed, Embase, Scopus, and Web of Science databases were queried for relevant literature, including articles, reviews, and clinical studies published till 2023. Search terms utilized encompassed "heart failure," "emerging therapies," "pharmacological advancements," "device-based interventions," "regenerative medicine," and

"precision medicine," employed in various combinations to capture pertinent publications.

### Inclusion and Exclusion Criteria

Inclusion criteria were defined to select literature aligning with the scope of this narrative review, emphasizing studies focusing on emerging therapies in heart failure management. Priority was given to articles critically assessing the impact of emerging therapies on clinical practice, covering pharmacological innovations, device-based interventions, regenerative medicine, and precision medicine. Exclusion criteria were applied to non-English publications, non-peer-reviewed articles, and studies devoid of clinical relevance or focused solely on basic science research.

### Data Synthesis

Data synthesis entailed categorization of emerging therapies into thematic groups, including pharmacological advancements, device-based interventions, regenerative medicine, and precision medicine. Each category underwent individual analysis to summarize therapy mechanisms, clinical efficacy, strengths, and limitations based on the included literature.

### Understanding Heart Failure

Heart failure is a complex clinical syndrome characterized by the heart's inability to effectively pump blood to meet the body's metabolic demands, resulting in inadequate circulation and oxygen delivery. It is a major global health concern impacting millions of individuals and challenging healthcare systems [9]. This narrative review provides an extensive overview of heart failure, including its definition, epidemiology, classification, pathophysiology, and emerging therapeutic strategies.

### Epidemiology of Heart Failure

Heart failure affects a substantial portion of the global population, with increasing prevalence driven by aging populations and rising rates of risk factors such as hypertension, diabetes, and obesity [10]. In the United States alone, approximately 6.2 million adults aged 20 and older were estimated to have heart failure in 2019 [11]. The prognosis of heart failure varies based on severity and underlying etiology, with significant mortality rates observed, particularly in advanced cases [11].

The economic burden of heart failure is also noteworthy, with substantial costs associated with hospitalizations, interventions, and long-term management. In the United States, the direct and indirect costs of heart failure exceeded \$30 billion in 2012 [12].

### Classification of Heart Failure

Heart failure is classified based on ejection fraction into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The European Society of Cardiology introduced a third category known as heart failure with mid-range ejection fraction (HFmrEF) to address the heterogeneous nature of the disease [13].

### Pathophysiology

Heart failure involves complex changes in the heart's structure and function, including left ventricular remodeling, diastolic dysfunction, and neurohormonal activation. Left

ventricular remodeling, often triggered by conditions like myocardial infarction and hypertension, can impair contractility and reduce stroke volume <sup>[14]</sup>. Neurohormonal activation, particularly involving the renin-angiotensin-aldosterone system and sympathetic nervous system, contributes to vasoconstriction, sodium retention, and increased cardiac workload <sup>[15]</sup>.

### Multifactorial Nature of Heart Failure

Heart failure is a syndrome resulting from various cardiac and non-cardiac conditions, including coronary artery disease, cardiomyopathies, valvular heart disease, arrhythmias, hypertension, diabetes, obesity, chronic kidney disease, and genetic factors <sup>[16]</sup>. These diverse etiologies contribute to the complexity of heart failure diagnosis and treatment.

In conclusion, heart failure is a multifaceted syndrome with significant clinical and economic implications. Understanding its epidemiology, classification, pathophysiology, and multifactorial nature is crucial for developing effective therapeutic strategies and improving patient outcomes.

### Current Treatment Landscape

The landscape of heart failure (HF) management has undergone significant evolution in recent decades, aiming to alleviate symptoms, enhance quality of life, reduce hospitalizations, and extend survival rates. Tailored treatment approaches distinguish between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). This section presents a comprehensive review of existing HF treatments, encompassing pharmacological interventions, device-based therapies, and lifestyle modifications. Additionally, it emphasizes the current limitations of these therapies, underscoring the urgent necessity for innovative strategies in HF management.

### Pharmacological Interventions

Angiotensin-converting enzyme (ACE) inhibitors, such as enalapril, lisinopril, and ramipril, have played a pivotal role in HFrEF treatment by inhibiting angiotensin II production. The landmark CONSENSUS trial highlighted enalapril's mortality-reducing effects in severe HF patients <sup>[19]</sup>. Angiotensin receptor blockers (ARBs), like losartan and valsartan, offer an alternative for ACE inhibitor-intolerant patients and demonstrate efficacy in reducing HF morbidity and mortality. Beta-blockers, including carvedilol and bisoprolol, antagonize catecholamines, improving cardiac function and reducing mortality rates. The CIBIS-II trial demonstrated bisoprolol's efficacy in HFrEF mortality reduction <sup>[20]</sup>. Mineralocorticoid receptor antagonists (MRAs) like spironolactone and eplerenone counteract sodium and water retention, with spironolactone showing mortality benefits in severe HFrEF (RALES trial, <sup>[20]</sup>).

Sacubitril/valsartan, combining a neprilysin inhibitor with an ARB, represents a breakthrough for HFrEF treatment, as evidenced by superior outcomes in cardiovascular mortality and HF hospitalizations compared to enalapril (PARADIGM-HF trial, <sup>[20]</sup>). Diuretics such as furosemide and hydrochlorothiazide are crucial for fluid overload management but pose risks of electrolyte imbalances and renal dysfunction with prolonged use. Digoxin and ivabradine offer additional therapeutic options for specific

HF cases, particularly in rate control and symptomatic relief <sup>[20]</sup>.

### Device-Based Therapies

Implantable cardioverter-defibrillators (ICDs) are recommended for high-risk HFrEF patients prone to life-threatening arrhythmias. Cardiac resynchronization therapy (CRT) benefits HFrEF patients with intraventricular conduction delays, enhancing symptom control and reducing mortality rates. Left ventricular assist devices (LVADs) serve as bridge therapy or destination therapy for transplant-ineligible patients <sup>[21]</sup>.

### Heart Transplantation

Heart transplantation remains the definitive therapy for end-stage HF, albeit limited by organ availability.

### Lifestyle Modifications and Non-Pharmacological Approaches

Dietary sodium restriction and fluid management are critical components of HF care, while weight management and exercise are essential for symptom control and improved quality of life. Smoking cessation and alcohol restriction are emphasized to prevent further myocardial damage <sup>[17, 18]</sup>.

### Limitations of Current Therapies

Despite significant advancements, many therapies have limited efficacy in HFpEF, and side effects like hypotension and renal dysfunction necessitate careful monitoring. Device-based therapies carry risks of complications, while heart transplantation faces donor organ shortages and cost barriers <sup>[22]</sup>.

### Ongoing Need for Innovation

Precision medicine, biomarker-based approaches, regenerative therapies, and telemedicine hold promise in enhancing HF management by tailoring treatments, enabling early intervention, and predicting disease exacerbations <sup>[23, 24]</sup>. Continued research into novel pharmacological agents and advancements in mechanical support devices and artificial intelligence are essential to address the multifaceted challenges posed by HF and improve patient outcomes.

This narrative review underscores the evolving landscape of HF management, highlighting current therapeutic approaches' benefits and limitations while advocating for ongoing innovation to optimize care delivery and patient outcomes in this complex syndrome.

### Pharmacological Innovations

Heart failure is a prevalent and complex cardiovascular syndrome with a significant global burden. Despite advancements in treatment options, managing heart failure remains challenging due to its multifactorial etiology and varied clinical presentations. In recent years, pharmacological innovations have significantly improved the prognosis and quality of life for heart failure patients. This section reviews the latest advancements in pharmacological therapies, highlighting novel drug classes, mechanisms of action, and key findings from clinical trials.

### Novel Drug Classes

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, originally developed for diabetes mellitus treatment, have emerged as groundbreaking therapies in heart failure

management. Drugs such as empagliflozin, dapagliflozin, and canagliflozin inhibit glucose reabsorption in renal tubules, leading to glycosuria and improved glycemic control. Beyond diabetes, SGLT2 inhibitors offer cardiovascular benefits by promoting diuresis, reducing blood volume, improving myocardial energetics, and reducing oxidative stress and inflammation [25].

Angiotensin receptor-neprilysin inhibitors (ARNIs) like sacubitril/valsartan represent another innovative class. Sacubitril inhibits neprilysin, increasing natriuretic peptides that promote vasodilation and diuresis. Combined with valsartan's angiotensin receptor blockade, sacubitril/valsartan reduces cardiovascular mortality and heart failure hospitalizations [26].

Vericiguat, a soluble guanylate cyclase (sGC) stimulator, enhances cyclic guanosine monophosphate (cGMP) production, promoting vasodilation and reducing myocardial hypertrophy. The VICTORIA trial demonstrated reduced cardiovascular death and heart failure hospitalization with vericiguat in heart failure patients [27].

### Mechanistic Insights

SGLT2 inhibitors promote diuresis by inhibiting glucose reabsorption, decrease oxidative stress and inflammation, and improve endothelial function and cardiac efficiency [25]. Sacubitril/valsartan increases natriuretic peptide levels, leading to vasodilation and reduced ventricular remodeling [26]. Vericiguat restores nitric oxide (NO) signaling, reducing afterload and improving diastolic function [27].

### Clinical Implications and Guidelines

The transformative impact of these drugs has led to updated guidelines. SGLT2 inhibitors are recommended in heart failure with reduced ejection fraction (HFrEF), regardless of diabetes status, to reduce cardiovascular risk [28]. Sacubitril/valsartan is recommended over ACE inhibitors or ARBs for symptomatic HFrEF patients [28]. These guidelines reflect the drugs' potential to enhance heart failure outcomes.

### Challenges and Considerations

Despite benefits, cost and patient selection challenges exist. Ensuring affordability and education on benefits and risks are vital for optimizing therapy outcomes [29].

### Device-based Interventions in Heart Failure Management

In addition to pharmaceutical innovations, device-based interventions have played a crucial role in advancing heart failure management. These interventions encompass a spectrum of technologies, including implantable devices, remote monitoring systems, and applications of artificial intelligence (AI). This section reviews the impact of innovative devices on heart failure management and their implications for patient outcomes.

#### Implantable Devices

Cardiac Resynchronization Therapy (CRT) involves implanting a specialized pacemaker capable of pacing both the left and right ventricles simultaneously. CRT is primarily indicated for heart failure patients with ventricular dyssynchrony, characterized by delayed or uncoordinated contraction of the ventricles [30]. By synchronizing ventricular contraction, CRT optimizes cardiac function and

has shown significant benefits in patients with left bundle branch block or intraventricular conduction delays [31]. Studies have demonstrated improvements in symptoms, exercise capacity, and quality of life in heart failure patients, particularly those with reduced ejection fraction (HFrEF) [31, 32]. Additionally, CRT reduces hospitalizations and mortality in eligible candidates [32].

Implantable Cardioverter Defibrillators (ICDs) are electronic devices that continuously monitor the heart's rhythm and deliver high-energy electrical shocks to terminate life-threatening ventricular arrhythmias. ICDs have substantially reduced the risk of sudden cardiac death in high-risk patients, such as those with prior myocardial infarction or symptomatic heart failure [33].

#### Ventricular Assist Devices (VADs)

Ventricular Assist Devices are mechanical pumps implanted in patients with advanced heart failure as a bridge to transplant or destination therapy. VADs augment cardiac output by assisting the weakened heart in pumping blood from the left ventricle to the aorta. They have revolutionized the management of end-stage heart failure and significantly improved survival and quality of life in patients not suitable for heart transplantation [34].

#### Remote Monitoring

Remote patient monitoring (RPM) utilizes technology to track patient health status and transmit data to healthcare providers without frequent in-person visits. RPM enables proactive monitoring of vital signs, symptoms, and medication adherence, leading to reduced hospitalizations and improved outcomes in heart failure patients [35].

#### Implantable Hemodynamic Monitors

Implantable hemodynamic monitors continuously measure pulmonary artery pressures, providing real-time data on a patient's hemodynamic status. These monitors have been associated with reduced heart failure hospitalizations by facilitating timely interventions based on changes in pressure readings [36].

#### Artificial Intelligence Applications

Machine learning (ML) and natural language processing (NLP) are emerging tools for risk prediction and clinical decision support in heart failure management. ML algorithms analyze large datasets to identify high-risk patients who may benefit from intensive monitoring or interventions. NLP extracts valuable insights from unstructured clinical notes, enhancing the depth and quality of clinical assessments [37, 38].

#### Clinical Implications and Guidelines

Device-based interventions and AI applications have introduced transformative approaches to heart failure management. Clinical guidelines emphasize the importance of multidisciplinary heart failure teams in evaluating patients for device therapy and integrating remote monitoring data into clinical workflows. As AI technologies mature, guidelines are expected to evolve to incorporate specific recommendations for AI use in heart failure management.

Despite promising outcomes, challenges remain in ensuring equitable access to these technologies, addressing data security concerns, and integrating device-based

interventions and AI applications into routine clinical practice. Continuous evaluation of their impact on patient outcomes is crucial to optimize their clinical utility and ensure tangible benefits in heart failure management.

### **Regenerative Medicine and Stem Cell Therapy in Heart Failure**

Heart failure poses a significant global health challenge characterized by impaired cardiac function and debilitating symptoms. Conventional treatment options for advanced heart failure remain limited<sup>[39]</sup>. In recent years, regenerative medicine and stem cell therapy have emerged as promising strategies to address this unmet medical need<sup>[40]</sup>.

#### **Stem Cells and Cardiac Regeneration**

Stem cells possess the unique capability to differentiate into diverse cell types and promote tissue repair. Embryonic stem cells (ESCs), derived from early-stage embryos, have shown potential in generating new cardiomyocytes and improving cardiac function<sup>[41]</sup>. Despite ethical concerns associated with ESCs, induced pluripotent stem cells (iPSCs) represent a promising alternative. iPSCs can be derived from a patient's own cells and differentiated into cardiomyocytes, offering personalized regenerative therapies<sup>[42]</sup>.

Mesenchymal stem cells (MSCs), sourced from various tissues, exhibit paracrine effects that modulate inflammation, promote angiogenesis, and stimulate endogenous cardiac repair mechanisms<sup>[43]</sup>. Clinical trials investigating MSC-based therapies have reported encouraging safety profiles and functional improvements in heart failure patients<sup>[44]</sup>.

Cardiac progenitor cells (CPCs), a specialized subset of stem cells within the heart, have demonstrated the potential to differentiate into cardiomyocytes and promote tissue repair in early-phase clinical trials<sup>[45]</sup>.

#### **Current Status of Stem Cell Therapy in Heart Failure**

While numerous clinical trials have demonstrated the safety and feasibility of stem cell-based interventions in heart failure, the outcomes have varied across studies<sup>[46]</sup>. Factors such as cell type, delivery method, and patient selection criteria influence treatment responses. Long-term efficacy and durability of stem cell-based interventions necessitate further investigation<sup>[47]</sup>.

#### **Future Directions in Stem Cell Therapy**

Future research directions aim to optimize stem cell therapy for heart failure treatment. Advances in iPSC technology enable disease modeling and personalized approaches to heart regeneration. Combining stem cells with biomaterials and tissue engineering techniques holds promise for creating functional cardiac patches or constructs. Additionally, exploring synergies with gene therapy, growth factors, or pharmacological agents may enhance regenerative effects and improve outcomes.

In conclusion, regenerative medicine and stem cell therapy represent innovative approaches to address the complex challenges of heart failure treatment. Ongoing research endeavors aim to overcome current limitations and pave the way for personalized and effective therapies.

#### **Clinical Implementation and Challenges**

Implementing emerging therapies in heart failure management poses significant challenges across multiple domains, including cost, accessibility, and ethical considerations. The integration of innovative medical treatments into clinical practice requires overcoming hurdles that influence their successful adoption within the healthcare ecosystem. A primary challenge is the substantial financial burden associated with developing and manufacturing novel therapies. Pharmaceutical companies invest substantial resources in research, preclinical studies, and rigorous clinical trials, which ultimately contribute to the high cost of these therapies. Furthermore, the manufacturing complexities of emerging therapies, such as gene and personalized medications, can drive up production costs and present logistical challenges.

Despite gaining regulatory approval, these therapies often face delays in reimbursement approval and evaluation of cost-effectiveness, which can hinder patient access. The high cost of emerging therapies can lead to significant out-of-pocket expenses for patients, exacerbating healthcare disparities by limiting access for vulnerable populations, such as lower-income individuals. These challenges underscore the need for innovative strategies to address cost barriers and ensure equitable access to emerging heart failure treatments.

#### **Access Challenges**

Achieving equitable access to emerging heart failure therapies is another critical challenge in healthcare. Geographic disparities can significantly impact access, with patients in urban areas typically having greater access compared to those in rural or underserved regions. Comprehensive insurance coverage plays a pivotal role in facilitating patient access to these therapies, yet disparities persist among patients with limited or no insurance. Additionally, disparities in clinical trial participation further limit access for underrepresented populations, highlighting the need for targeted interventions to improve inclusion.

Navigating regulatory pathways and securing reimbursement approvals post-regulatory approval can further restrict patient access, particularly for those with urgent medical needs. The specialized expertise required for delivering emerging therapies may not be universally available, necessitating patient travel to centers of excellence. Addressing these access challenges requires collaborative efforts among healthcare stakeholders to enhance infrastructure, expand insurance coverage, and improve inclusivity in clinical research.

#### **Ethical Considerations**

The ethical dimensions of implementing emerging heart failure therapies are complex and demand careful consideration. Obtaining informed consent is fundamental, yet challenging given the novelty and complexity of these therapies. Protecting patient data privacy and ensuring transparency in data usage are critical ethical imperatives, given the sensitive nature of genetic and health information involved.

Decisions about the allocation of limited healthcare resources, including emerging therapies, must prioritize fairness and equity to minimize disparities. Ethical frameworks emphasizing patient well-being and equitable access should guide decision-making by healthcare providers, researchers, and policymakers. Ongoing

monitoring and transparency regarding potential risks and benefits are essential to uphold ethical principles of non-maleficence and justice.

Addressing the challenges associated with implementing emerging therapeutic strategies in heart failure management requires multifaceted approaches that consider cost, accessibility, and ethical considerations. Collaborative efforts among healthcare stakeholders are essential to ensure equitable access and responsible implementation of these promising therapies.

### Conclusion

In summary, this narrative review has elucidated the multifaceted landscape of heart failure management, elucidating its intricacies, obstacles, and promising innovations. The insights gleaned underscore the transformative impact of ongoing progress in heart failure therapeutics. These advancements bring optimism to patients grappling with this complex condition, ranging from novel pharmaceutical interventions to inventive device-oriented therapies, regenerative medicine, and personalized care strategies. They empower tailored treatment protocols, precise risk assessment, and a shift toward patient-centric care models. The integration of data-informed clinical decision-making, interdisciplinary cooperation, and patient engagement holds the promise of improved outcomes and heightened quality of life for those affected by heart failure.

Amidst the challenges posed by cost, accessibility, and ethical considerations, it becomes evident that the pursuit of emerging therapies and precision medicine in heart failure management transcends scientific exploration to represent a moral imperative. The future of heart failure care stands poised to redefine patient experiences, mitigate healthcare disparities, and ultimately, preserve lives. With sustained research efforts and unwavering commitment, a brighter horizon emerges for heart failure patients, ushering in a transformed landscape of care.

### Conflict of Interest

Not available

### Financial Support

Not available

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