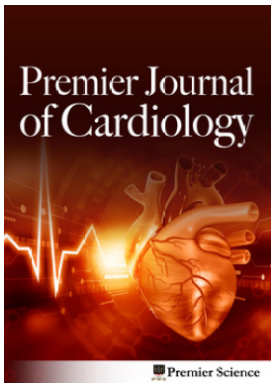

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Recent Advancements in the Management of Heart Failure: A Review

Saheed Ekundayo Sanyaolu

ABSTRACT

Heart failure is associated with considerable morbidity and mortality, resulting in high healthcare expenditure worldwide. The last decade has witnessed several significant developments and advances in the management of heart failure. To ensure rapid access to a concise overview of existing evidence for clinical decision-making regarding heart failure management, this study aimed to review scientific publications on emerging treatment approaches for heart failure, particularly in the last 10 years. Scientific databases, including PubMed, Scopus, Web of Science, and Cochrane Library, were explored for research articles on the advances in the management of heart failure and its comorbidities. A narrative review approach was employed in this report. Heart failure has multiple etiologies; hence, a critical aspect of its management involves the identification and treatment of the cause, which may include structural defects in the heart or pathologies from other parts of the body. Notable criteria for the classification of heart failure or for risk stratification are classification with the degree of ejection fraction and the New York Heart Association classification of heart failure. Challenges of traditional treatment strategies comprised lack of precision, treatment failure, adverse treatment outcomes, and short survival. In recent years, new drugs have been tested and approved for heart failure management, and some of them are included in the treatment guidelines for heart failure. Furthermore, precision medicine through genome editing and artificial intelligence-based innovations have revolutionized the management of healthcare. However, there are emerging concerns regarding the affordability and accessibility of the new treatment strategies.

Keywords: Heart failure management, Precision medicine, Genome editing, Artificial intelligence, Regenerative therapy

Highlights

- Challenges of traditional treatment strategies included lack of precision, treatment failure, adverse treatment outcomes, and short survival.
- In recent years, multiple pharmacological agents have been added to the pool of drugs for heart failure management.
- Other advances in heart failure management are novel medical devices, genome editing, regenerative therapy, and precision medicine.

Introduction

With an aggregate of about 17.9 million global mortality rates yearly, cardiovascular diseases—ischemic heart disease, myocardial infarction, stroke, and heart failure—are ranked one of the leading causes of death worldwide.[1] Like other cardiovascular diseases, heart failure is associated with high mortality and morbidity rates, among other impacts on individual and population health outcomes. The Global Burden of Disease Study estimated the prevalence of heart failure to be at least 64 million globally;[2] this translates to about 2% of the general population in the United States, Canada, and European countries.[3] In terms of financial burden, the direct healthcare cost due to the management of heart failure is expected to increase to 69.8 billion USD by 2030 in the United States alone.[4]

An upward trend has been associated with heart failure prevalence mainly due to the aging population and the development of novel management approaches, resulting in longer overall survival for patients with the condition.[5] However, heart failure also severely affects the younger population; Yang et al.[6] estimated that about 148 of 100,000 adolescents and young adults suffered from heart failure globally in 2021. These staggering statistics underscore the severe consequences of heart failure on overall health outcomes and the need for more effective management strategies for the condition.

Previous studies have highlighted multiple developments in the management of heart failure, comprising highly sensitive diagnostic approaches and treatment strategies.[7,8] These developments were designed to address specific patient needs, and varying treatment outcomes have been attributed to them. However, clinical decision-making regarding the management of life-threatening conditions such as heart failure often requires access to prompt and concise overviews of available evidence regarding multiple treatment approaches. Hence, this study aimed to review studies on recent advancements in the management of heart failure.

Heart Failure

Heart failure has multiple etiologies, and it causes different clinical symptoms based on the type of heart failure; hence, many definitions exist for heart failure based on different criteria. In a bid to develop a universal definition, the Heart Failure Society of America (HFSA), the Heart Failure Association of the European Society of Cardiology (ESC), the Japanese Heart Failure Society, and the Writing Committee of the Universal Definition of Heart Failure[9] proposed the following definition:

"*heart failure is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.*"

This definition recognizes the fact that heart failure is not a singular clinical condition but a manifestation of multiple symptoms. Common etiologies and

objective assessment parameters are also incorporated into this definition.

Based on its pathophysiology, heart failure is considered a sequela of ventricular dysfunction. The left ventricle pumps oxygenated blood from the lungs to the body, while the right ventricle sends deoxygenated blood from the body to the lungs. Heart health is reflected in its ability to pump blood. Therefore, the 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/HFSA Guideline for the Management of Heart Failure utilized the measure of blood pumped by the heart per beat, known as the ejection fraction, particularly that of the left ventricle, to classify heart failure: (1) heart failure with reduced ejection fraction (HFrEF; ≤40% ejection fraction), (2) heart failure with preserved ejection fraction (HFpEF; ≥50%), and (3) heart failure with mildly reduced ejection fraction (41–49%).[10] This classification is critical to the treatment planning for heart failure.

Etiologies and Clinical Manifestation

Heart failure is characterized by multiple etiologies that are broadly categorized as cardiac and noncardiac causes.[11] Cardiac causes are those structural abnormalities originating from the heart itself, including ischemic heart disease (also known as coronary artery disease), valvular disorders, congenital heart defects, genetic heart disorders, and myocarditis.[12] Additionally, cardiac causes may also arise from drugs (including chemotherapeutic drugs) and toxin ingestion. Contrastingly, noncardiac causes are etiologies that arise from other parts of the body but ultimately increase cardiac workload, leading to a progressive decline in heart functions.[13] Commonly, these include chronic metabolic disorders such as hypertension, diabetes mellitus, thyroid diseases, and anemia. Furthermore, respiratory diseases and renal insufficiency may also be categorized as noncardiac causes of heart failure.[14] Similar to cardiac causes, noncardiac causes may also be precipitated by drugs and toxins.[11]

Reduction in ejection fraction, as observed in heart failure, causes fluid accumulation in the lungs, liver, and other parts of the body. This fluid build-up or congestion, which causes various symptoms, including dyspnea, edema, palpitations, ascites, fatigue, and limitations in physical activities, informed the naming of the condition as "congestive heart failure."[12]

The classification of heart failure based on the severity of symptoms, as delineated by the New York Heart Association,[15,16] provides a concise overview of the clinical manifestation of the condition (Figure 1).

Depending on the stage of the disease, heart failure increases the risk of stroke, arrhythmias, chronic kidney disease, pulmonary edema, chronic obstructive pulmonary disorder, and cardiomegaly.[11] Patients with heart failure often suffer poor prognoses except when the disease's etiology is reversible.

Conventional Management Approaches

Clinical Diagnosis

Effective management of heart failure relies on early detection. Moreover, given that previous adverse cardiovascular events are major risk factors for heart failure, a patient's medical history plays a key role in diagnosis. A patient showing any of the symptoms explained in Figure 1 and with a medical history of adverse cardiovascular events and/or other risk factors of heart failure should be referred for a comprehensive assessment. Diagnosis of heart failure typically involves physical examination to determine if the patient is showing any symptoms of poor perfusion (cyanosis), hypotension, confusion, or edema, among others.[17] This may then be followed by chest X-ray, electrocardiography, echocardiography, imaging tests (including magnetic resonance imaging and computed tomography), and blood tests.[17]

Serum B-type natriuretic peptide (BNP) is an important biomarker for heart failure because its level increases in the body in response to increased cardiac workload.[18] Hence, this assessment may be important

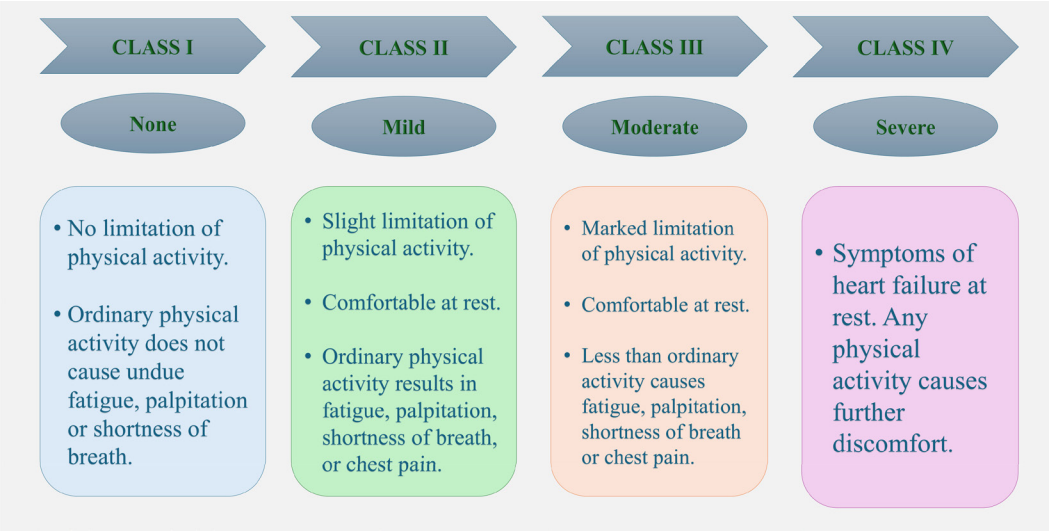

Fig 1 | New York heart association classification of heart failure

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for differential diagnosis in patients with dyspnea, a condition that could be caused by other conditions aside from heart failure. Other blood tests that may be required include complete blood count and kidney, liver, and thyroid function tests.[17]

Diagnosis-Related Challenges

Notably, the symptoms of heart failure are not always noticeable, and some are detected after considerable disease progression. Hence, it is essential that patients with previous adverse cardiac events and those at high risk of heart failure are monitored to ensure early detection. Additionally, symptoms exhibited by patients are not always specific to heart failure, thereby necessitating comprehensive differential diagnosis.

Given the need for swift clinical interventions, particularly in acute heart failure, any delay in the aforementioned tests can greatly impact patients' treatment outcomes and mortality risk.[19] Similarly, given that treatment plans are designed based on the stage of heart failure and risk stratification, the availability of multiple classification criteria and management guidelines could cause confusion and inconsistencies in the therapeutic approach. This may lead to disease progression and rehospitalizations. Furthermore, public health challenges such as long waiting times, limited access to specialized healthcare, and out-of-pocket payment for health services may affect the promptness and accuracy of diagnosis.[20]

Conventional Treatment Strategies

The management of heart failure comprises lifestyle modification, identification and control of the root cause, pharmacological interventions, and surgical interventions.[19] To reduce fluid accumulation in the body, a classic symptom of heart failure, dietary limitation of sodium intake and electrolyte replacement therapy may be undertaken. Additionally, conditions such as obesity, diabetes, anemia, hypertension, atherosclerosis, and myocardial infarction should be addressed.[18]

Traditionally, classes of drugs used in the management of heart failure include diuretics, beta-blockers, vasodilators, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, vasopressors, inotropic drugs, and opioids.[11] Specific drugs in each class are indicated in Figure 2.

Evidence supporting the use of some of these drugs is limited, while some are only used in special cases because of the risk of adverse effects. For instance, in a meta-analysis conducted by Gao et al.,[21] opioids were found to be associated with increased mortality in patients with acute heart failure. This is corroborated by the midazolam versus morphine in acute cardiogenic pulmonary edema (MIMO) trial, which compared the safety and efficacy of morphine with those of midazolam in patients with atrial fibrillation; evidence from the study suggests that morphine has a higher risk of adverse events.[22] Furthermore, Sethi et al.[23] reported that while digoxin showed better efficacy compared to placebo, its effect was inferior to that of beta-blockers. The study also stressed the fact that limited evidence exists regarding the long-term effects of digoxin. These findings underscore the need for novel pharmacological agents with improved efficacy and tolerable safety profiles.

A notable complication of heart failure occurs when the cardiac dysfunction has progressed to the extent that the heart pumping function is insufficient to meet the body's requirements, resulting in peripheral hypoperfusion and organ damage; this is known as cardiogenic shock, and it is associated with poor survival outcomes.[24] Acute management of this condition involves the use of inotropes and vasopressors. To improve cardiovascular functions, inotropes, such as dobutamine, milrinone, and levosimendan, increase the contractility of the heart, while vasopressors, such

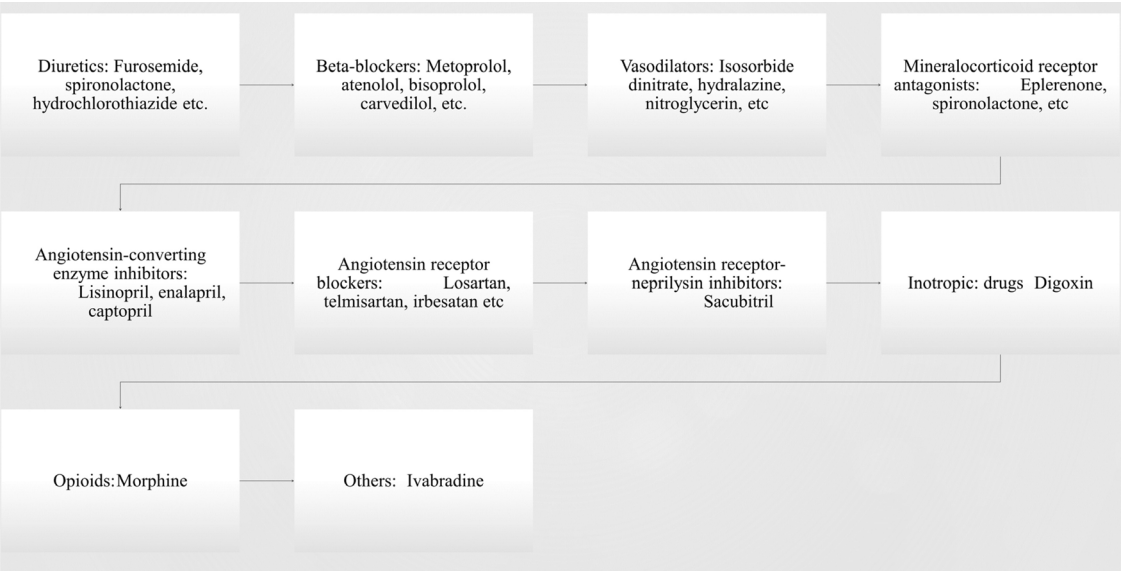

Fig 2 | Classes of drugs used for heart failure

as norepinephrine, epinephrine, and phenylephrine, induce vasoconstriction and increase peripheral resistance.[25] An international multidisciplinary panel of experts recommended norepinephrine and dobutamine as first-line vasopressor and inotrope, respectively.[26]

Valvular repair or replacement is a common example of a surgical approach in the traditional management of heart failure. This is important in patients whose etiology is valvular disorder. Similarly, coronary artery bypass grafting may be performed in patients with heart failure secondary to coronary artery disease. The procedure bypasses the narrowed or obstructed artery in a bid to promote revascularization of the heart. Ultimately, in extreme cases, particularly in young, otherwise healthy patients, a total heart transplant may be required.

Treatment-Related Challenges

Studies have highlighted multiple challenges in conventional management strategies for heart failure. Butler et al.[27] highlighted the need for tailoring the therapeutic approach to individual patients' characteristics rather than the characteristics of a class or stage of heart failure. The authors also noted that the available management approach tends to focus solely on the inpatient management of heart failure. Heart failure is a chronic condition requiring continuous management; hence, after discharge of patients from the hospital, the treatment plan should delineate approaches to ensure that patients continue lifestyle modifications and use prescribed medications as recommended.[28] Furthermore, continuous monitoring and follow-up of patients are essential to treatment outcomes.

Impaired cognition, a common clinical manifestation of heart failure, has also been highlighted as a potential barrier to effective treatment.[8] Heart failure management often requires titration of drugs based on patient response, and patients receive counseling regarding this to improve their self-care capacity. However, a patient with cognitive impairment may find this difficult. This emphasizes the critical role of caregivers and support systems.[8] Harmonization of diagnostic criteria and treatment guidelines is also essential to reduce confusion and promote consistency.

Advancements in the Management of Heart Failure

Clinical Assessments

Biomarkers

Although serum BNP and N-terminal pro-BNP are used conventionally for heart failure diagnosis, a high or low level of serum BNP is not a definite indicator of the presence or absence of heart failure, respectively.[18] Hence, various other potential biomarkers have been investigated for this purpose.

Carbohydrate antigen 125 (CA 125), also known as mucin 16, is a glycoprotein that is used in cancer diagnosis, especially ovarian cancer.[29] Recent evidence has indicated an elevation of CA 125 serum levels in congestion and inflammation in the body. In a clinical trial, Núñez et al.[30] reported that high levels of CA 125 were directly correlated with symptoms of heart failure as well as clinical outcomes, including hospital readmission and death. This highlights the importance of CA 125 in prognostication and risk stratification for patients with heart failure.

Another investigated biomarker for heart failure is soluble ST2 from the interleukin-1 receptor family. It is an indicator of mechanical stress and fibrosis in cardiomyocytes. Riccardi et al.[31] highlighted that, unlike serum BNP biomarkers, soluble ST2 shows lower variations with age, sex, and some physiological processes in the body, allowing for the establishment of a constant threshold for diagnosis. In a randomized controlled trial,[32] patients with HFrEF after acute decompensation were stratified into two groups to receive soluble ST2-guided therapy and standard therapy, respectively. After 6 months, compared to standard therapy, soluble ST2-guided therapy improved left ventricular ejection fraction (LVEF) and patients' quality of life and reduced the incidence of poor clinical outcomes.

Furthermore, Galectin-3 is a proven indicator of fibrosis and anatomical remodeling. Galectin-3 has been found to be reflective of the early stages of inflammatory processes in the body, and this could aid the development of therapeutic agents at this stage of pathogenesis.[33] However, the expression of Galectin-3 is not specific to the heart; it has been found to be elevated in other inflammatory diseases, including autoimmune and neurodegenerative diseases.[34]

Other biomarkers that are being utilized/investigated for their potential roles in the pathogenesis of heart failure include procalcitonin,[35] neutrophil gelatinase-associated lipocalin,[36] and mid-regional pro-atrial natriuretic peptide.[18]

Global Longitudinal Strain (GLS)

GLS, measured through echocardiography, tracks muscle movement to assess the contractility of the heart in the longitudinal direction during each cardiac cycle.[37] This is particularly important for the diagnosis of HFpEF. The Copenhagen City Heart Study, a longitudinal study with an average follow-up period of 11 years, found that low GLS was significantly associated with the incidence of heart failure, among other cardiovascular diseases. Findings from the study highlighted the roles of GLS in the determination of long-term risk cardiovascular diseases.[37]

Artificial Intelligence (AI)-Based Diagnosis

AI has revolutionized various fields in health management; AI-based advancements in medicine include robot-assisted surgery, machine learning models for disease prediction and treatment planning, as well as AI-based drug discovery and development.[38] An example of these advancements in heart failure management is the AI-Clinical Decision Support System, a machine learning innovation that assists physicians in the diagnosis of heart failure.[39] The system uses patients' information, such as physical evaluation results, echocardiographic findings, and findings from other tests, to predict heart failure diagnosis and the

associated ejection fraction. The system showed a 98% concordance rate with heart failure specialists. Furthermore, machine learning models have also been developed for risk stratification[7] and prediction of treatment outcomes[40] in patients with heart failure.

Novel Treatment Strategies

Pharmacological Interventions

Pharmacological agents for the management of heart failure have accumulated over the years. An example of new drug classes used for heart failure management is sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Although originally developed for the management of type 2 diabetes, SGLT-2 inhibitors have been shown to reduce the risk of death and hospitalization in patients with heart failure regardless of the presence or absence of comorbidity with diabetes.[41] The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure[41] and Empagliflozin in Heart Failure (EMPEROR)[42] trials are notable for the assessment of the impacts of dapagliflozin and empagliflozin, respectively, on cardiovascular outcomes.

The favorable outcomes of the drugs, as reported in these trials, prompted the inclusion of the drugs in the list of drugs used for heart failure management. SGLT-2 inhibitors, alongside three other traditional drug classes—beta-blockers, angiotensin receptor blockers + angiotensin receptor-neprilysin inhibitors, and mineralocorticoid receptor antagonists—are known as the foundational drugs for heart failure. Recent international guidelines for heart failure management, including the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure[17] and the 2022 AHA/ACC/HFSA guideline for the management of heart failure,[10] recommend the use of these drugs. Although previous treatment guidelines encouraged stepwise inclusion and up-titration of doses of these drugs based on the severity of heart failure, newer guidelines now recommend starting all four foundational drugs as soon as possible for patients.[43] The rationale for this is that the drug classes act by different mechanisms, and together, they elicit an additive response.[44] Notwithstanding, the peculiar characteristics and tolerance of each patient must be considered when introducing these drugs.[45]

Various other drugs have been evaluated for heart failure management, including omecamtiv mecarbil, which belongs to the cardiac myosin activators class and acts directly on cardiac muscle to improve contractility and systolic function.[46] The Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure trial investigated omecamtiv mecarbil and reported a slightly lower incidence of adverse events with omecamtiv mecarbil compared to placebo.[46] While this is promising, further research efforts are needed to substantiate this finding.

Another example of a novel drug for heart failure management is vericiguat. Vericiguat is a soluble guanylate cyclase stimulator that causes vasodilation and improves blood flow.[47] The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction trial reported a modest reduction in the incidence of death and hospitalization in patients with heart failure who were administered vericiguat for approximately 11 months compared to those who received the placebo.[47]

Heart rate is a proven prognostic factor of heart failure, and elevated resting heart rate is associated with poor outcomes. Increased heart rate is a common finding in patients with heart failure, as the reduced heart function induces a compensatory mechanism that results in tachycardia.[48] While beta-blockers are used to manage increased heart rate, lack of selectivity causes other unfavorable cardiovascular outcomes.[49] Ivabradine is a selective inhibitor of I_f current in the sinoatrial node, slowing down the heart rate and reducing cardiac workload. The SHIFT trial assessed treatment outcomes associated with ivabradine in comparison with placebo in patients with heart failure who had elevated heart rates ≥70 beats per minute and LVEF ≤35%.[50] Ivabradine resulted in an 18% reduction in the risk of cardiovascular death or hospital admission for worsening heart failure. Therefore, ivabradine is used clinically in heart failure therapy that requires heart rate reduction.

Given that obesity is a common risk factor for heart failure, especially in patients with preserved ejection fraction, novel weight-loss medications have been investigated for their roles in the management of HFpEF. Glucagon-like peptide-1 agonists are a class of drugs used in managing type 2 diabetes and weight management, and medications from this drug class have been evaluated for heart failure therapy.[51] Notable examples of these assessments are the STEP-HFpEF and SUMMIT trials. The STEP-HFpEF trial focused on semaglutide; in addition to causing higher reductions in body weight compared to placebo (13.3% vs. 2.6%), semaglutide increased the Kansas City Cardiomyopathy Questionnaire clinical summary scores (KCCQ-CSS) of patients (16.6 vs. 8.7 points), indicating fewer symptoms of heart failure and better quality of life.[52] Likewise, the SUMMIT trial demonstrated that tirzepatide use resulted in a lower incidence of cardiovascular deaths or worsened heart failure (9.9% vs. 15.3%) and increased KCCQ-CSS (19.5 vs. 12.7 points).[53] These findings emphasize the importance of semaglutide and tirzepatide in the long-term management of HFpEF.

Valvular Repair

Heart failure due to valvular disease has also received considerable research attention in recent years. The MITRA-FR and the COAPT are important trials that assessed the impact of the catheter-based device (MitraClip) procedure on the management of mitral valve regurgitation in patients with reduced left ventricular ejection.[54,55] The patients included in the study were those who remained symptomatic after the maximum doses of pharmacological treatments. The procedure, also known as the mitral transcatheter edge-to-edge repair, used the MitraClip to repair the mitral valve. The MITRA-FR trial, which included patients with severe mitral regurgitation, reported no significant difference

in the incidence of death and hospitalization between patients who underwent the procedure + standard treatment and those who received only standard treatment.[54] However, the COAPT trial, which included patients with moderate-to-severe mitral regurgitation, reported a lower incidence of hospitalization and mortality in the experimental group.[55]

Implantable Medical Devices

Despite the progress made in the pharmacological treatment of heart failure in recent years, considerable limitations still exist, including lack of drug specificity, patient nonadherence to medication regimen, and the need for continuous modulation of pathophysiological pathways. The use of medical devices aims to address some of these limitations.

Given the need for continuous monitoring of patient's physiological parameters, the CHAMPION trial investigated the use of a remote pulmonary artery pressure monitoring device (CardioMEMS) in the management of patients with heart failure. The control group received standard care alone.[28] In addition to improving symptoms, CardioMEMS reduced the rate of hospitalization in the group whose care was managed based on pulmonary artery pressure measurements from the device. The device is a wireless implantable hemodynamic monitoring system that uses radiofrequency signals to transmit measurements to healthcare providers. This device is FDA-approved and is included in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[10]

The implantable cardioverter defibrillator (ICD) is used in patients who are prone to life-threatening arrhythmias, and it delivers shock to the heart (like a conventional defibrillator) to reset heart rhythm. ICD reduces the risk of sudden cardiac death and all-cause mortality in patients with heart failure.[56] Similar to this, the Baroreflex Activation Therapy for Heart Failure trial reported that the inhibition of the sympathetic nervous system and activation of the parasympathetic nervous system caused by the implantable Barostim NEO system improved symptoms of heart failure.[57] The authors indicated that the system improved the exercise capacity and patients' quality of life. Subsequently, the device was approved in 2019 by the FDA for patients who continued to exhibit symptoms despite pharmacological treatments.

Similar to the use of ICDs, cardiac resynchronization therapy (CRT) involves the implantation of a biventricular pacemaker, which delivers electrical signals to the two ventricles to synchronize their contractions and improve cardiac function.[58] This is a long-term management approach for heart failure, and evidence supporting its use is available in the literature. Moss et al.[59] compared the efficacy of CRT+ICD against ICD alone in patients with cardiomyopathy and an ejection fraction of ≤30%, reporting that CRT+ICD reduced the incidence of all-cause mortality or heart failure events (17.2% vs. 25.3%). An alternative to this approach is bundle branch pacing, which targets the part of the heart responsible for propagating electrical signals from atrioventricular nodes to the ventricles. Hence, in patients with ventricular dysfunction due to the left bundle branch block, the left bundle branch may be targeted to synchronize ventricular contraction and improve cardiac function. This is known as left bundle branch pacing, and it is associated with better electrical resynchronization in this patient group.[60]

In severe heart failure or cardiogenic shock, mechanical circulatory support devices are critical to sustain cardiac and respiratory functions and ensure continuous organ perfusion. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) device is a common example of such devices and is used in the acute management of cardiogenic shock.[61] Cannulas from the device are introduced into the patient's body through a major vein and artery. Subsequently, the machine provides oxygenation to the blood and removes carbon dioxide. The EURO SHOCK trial, while challenged by the COVID-19 pandemic, reported that VA-ECMO reduced all-cause mortality in patients who received the procedure (43.8% vs. 61.1%) compared to those who received standard treatment.[62] However, the study also reported increased bleeding complications in those who received VA-ECMO. Similarly, the DanGer Shock trial assessed the use of a percutaneous microaxial flow pump, another acute mechanical circulatory support device that provides left ventricular support but relies on optimal functioning of the right side of the heart.[63] This device also reduced all-cause mortality but was associated with increased adverse events. Overall, these devices provide life-preserving outcomes, but treatment plans must encompass the prevention of adverse events.

Furthermore, in heart failure caused by left ventricle failure, also known as left-sided heart failure, a left ventricle assist device (LVAD) may be required. A series of LVAD devices have been researched, notable of which is the HeartMate series: HeartMate I (pusher-plate pump), HeartMate II (axial-flow pump), and HeartMate 3 (centrifugal-flow pump).[64] Each new HeartMate was designed to correct the limitations of the previous ones and provide improved outcomes. HeartMate 3 is the latest in the series, and it is a fully magnetically levitated centrifugal-flow LVAD. In the final report of the MOMENTUM 3 trial published in 2019, HeartMate 3 was reported to be superior to HeartMate II in terms of reduced frequency of pump replacement, reduced reoperation rates, and lower incidence of stroke or bleeding.[65]

Other medical device-based heart failure therapies include the use of pacemakers, cardiac contractility modulation, and the use of intra-aortic balloon pumps.[66] While these may be considered classical treatment approaches, many of them have received evidence-based improvements over the last decade.

Cardiac Transplantation

Heart transplantation is a curative treatment for end-stage heart failure, and it improves the functional status of patients and their quality of life. This approach commenced many decades ago, but it has

seen improvement in recent years. Challenges of cardiac transplantation included a limited pool of donors, graft rejection, and short survival rates.[67] To address this, studies have evaluated novel drugs to suppress the sensitization of recipients to the newly transplanted organs. Consequently, novel targeted monoclonal antibody drugs, including tocilizumab, clazakizumab, eculizumab, and daratumumab, have been researched to provide pharmacological desensitization, prevent organ rejection, and enhance survival.[68]

Previously, individuals with viral infections such as hepatitis C, human immunodeficiency virus, and the severe acute respiratory syndrome coronavirus 2 were ineligible to be organ donors. There were concerns about transmission of the infection to the recipients as well as the rapid proliferation of the virus due to the immunosuppressive state after organ transplantation. However, given advances in the management of these conditions and promising reports of curative therapies, various organ transplant societies are starting to accept the transplantation of organs from infected individuals.[69] In such cases, the non-infected recipient received prophylaxis treatment perioperatively to reduce the risk of transmission and the development of infection.[69]

Moreover, research efforts are underway on the transplantation of organs from animals to humans—xenotransplantation. Previous efforts in this regard led to an antigenic response in humans; however, the advances in the field of gene editing have made it possible to delete genes that could cause an antigenic response from the animal. Griffith et al.[70] reported the transplantation of a heart from a genetically modified pig. The patient survived for 2 months. However, on post-mortem clinical assessments, the observed changes were not consistent with typical rejection reactions; research is ongoing to determine the cause of structural abnormalities found in the organ. Notwithstanding, findings from studies such as this can serve as reference points for future research in xenotransplantation.

Regenerative Medicine

Structural remodeling and formation of scar tissues are critical pathological manifestations in heart failure; hence, research efforts are underway on the use of regenerative cells to repair damaged cardiac tissue and improve symptoms. The CCTRN CONCERT-HF trial combined bone marrow mesenchymal stromal cells and c-kit positive cardiac cells as a regenerative treatment for heart failure secondary to ischemic heart disease.[71] The participants underwent transendocardial injection of the regenerative cells and were monitored for up to 1 year. Findings from the study demonstrated improved clinical outcomes and reduced incidence of adverse events with the regenerative treatment. However, no observable changes were found in the structure or function of the left ventricle; hence, the authors concluded that the observed outcomes could be due to systemic or paracrine cellular mechanisms rather than direct repair in the cardiomyocytes.

Other regenerative cells are being investigated for heart failure management, and promising outcomes have been reported.[72,73] The ultimate goal of the research efforts in this area is to enhance regenerative ability in the heart tissues, thereby promoting cellular repair and resolution of symptoms of heart failure.

Genome Editing

Gene therapies, including the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based approaches, offer promising potential in the management of heart disease by targeting disease-specific mutations that are associated with cardiomyopathy.[74] Genome editing mechanisms have been used to prepare genetic models of heart disease to enable the identification of genetic defects. Furthermore, the identified mutations have aided the development of CRISPR/Cas 9 genetic material, which can be introduced into the heart to excise mutations and promote gene correction.[75]

Yin et al.[76] recently developed echogenic liposomes for the delivery of CRISPR/Cas9 complexes into rat heart models; this study recorded successful gene editing, holding promise for application in humans. Zinc finger nucleases and transcription activator-like effector nucleases, among others, are other genome editing approaches that have been investigated.[74]

However, various challenges have been highlighted, including delivery and targeting systems, immune response, and off-target effects. Additionally, ethical concerns exist regarding the use of gene editing in humans due to limited information on the possible adverse effects.[75]

Precision Medicine

Similar to the diagnosis of heart failure, management strategies for heart failure have also benefited from the advent of AI-based innovations. Through a retrospective analysis, Ayers et al.[77] designed a machine learning model to predict 1-year survival after heart transplantation in adult patients. The study reported improved performance in a machine learning model that combined deep neural networks, logistic regression, AdaBoost, and random forest algorithms compared to the performance of the individual algorithms. The models used preoperative parameters, making them potentially important in designing eligibility criteria for patients undergoing transplants and predicting which patients are more likely to have better outcomes.

Likewise, Kianmehr et al.[78] utilized a machine learning model to evaluate the impact and interactive effect of multiple therapies for different comorbidities—hypertension and type 2 diabetes—on the risk of heart failure. The author reported that baseline diastolic blood pressure impacted glycemic control: a high risk of heart failure was observed in patients undergoing intensive hypoglycemic treatment who had low baseline diastolic pressure (45–69 mmHg) compared to those who had moderate or high baseline diastolic pressure.

The utilization of AI in heart failure management aims to ensure that management approaches are tailored to patient needs and that treatment efforts result in

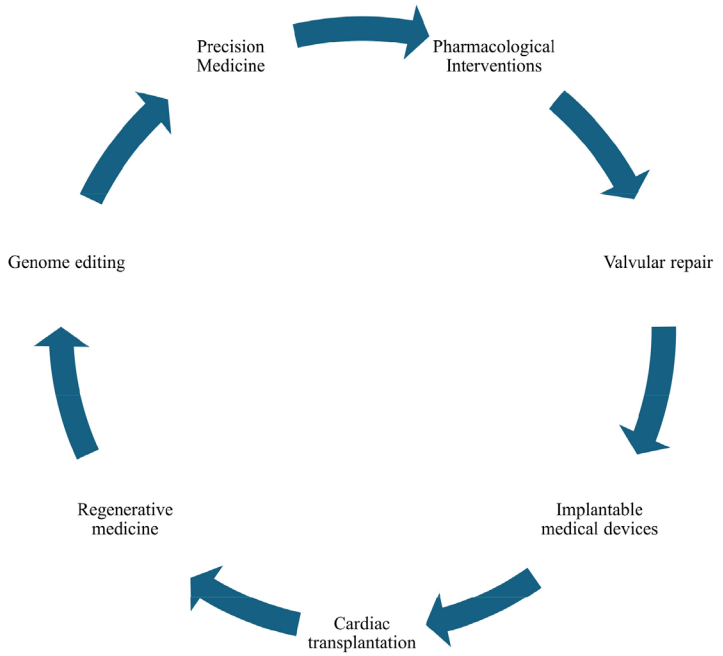

Fig 3 | New treatment strategies for heart failure

maximal efficacy with minimal adverse effects.[77] However, the importance of physician-supervised health management cannot be overemphasized; hence, it is essential that AI systems are designed to support clinicians in clinical decision-making rather than replace them. The novel treatment strategies are summarized in Figure 3.

Future Directions

Despite the impressive developments in different areas of heart failure management, continued efforts are needed to verify preliminary findings and develop new management strategies. Notably, research processes involved in the discovery of novel treatment strategies are resource-intensive. Hence, after approval from relevant regulatory authorities, the cost of such treatment is usually intimidating.[79] This limits the affordability of the treatments and makes it hard for patients to access them. A proposed solution for this is donations from individual donors, charities, and not-for-profit organizations.[80] Additionally, insurance companies are encouraged to expand the scope of their services so that the need for out-of-pocket payments can be reduced.

Various ethical dilemmas are also involved in experimental treatments. Given their novelty, limited scientific evidence exists regarding their effects. Hence, undergoing such treatments exposes patients to adverse effects and complications.[70] Moreover, publication bias, which favors the publication of positive results while the inherent risks are underreported, could also expose patients to health risks. Therefore, it is important that the research process and experimental reports are transparent and that patients are sufficiently educated on treatment risks before they are recruited for participation in experimental treatments.[79]

Precision medicine is an emerging theme in medicine, and relevant technological innovations should be leveraged to ensure that treatment strategies are tailored to specific patient characteristics. Innovations such as genetic profiling enable the identification of gene mutations responsible for various ailments, thereby promoting the development of targeted clinical interventions that ensure optimal health outcomes.[75] Additionally, evidence of the potential roles of AI innovations in clinical decision-making and treatment planning is extensive in the literature.[39,40] These innovations aid accurate disease diagnosis as well as promote the design of personalized treatments. The process of drug design and discovery also benefits from AI innovations through spatial visualization of chemical structures and swift screening of drug candidates.[78]

Conclusions

Various developments and milestones have been recorded in the management of heart failure in the past decade. This review provides a concise overview of the classical management approach and novel treatment strategies. Conventionally, heart failure is managed by a mix of lifestyle modifications, sodium and water restriction, control of primary disease, and treatment of symptoms. This typically involves the use of drugs and sometimes invasive clinical procedures. In recent times, new biomarkers have been discovered to aid in the early detection of disease and the monitoring of disease progression. Additionally, the pool of drugs used for the management of heart failure has increased with the inclusion of drugs with better efficacy and safety profiles. Consequently, treatment guidelines have been modified.

To ensure good treatment outcomes with drugs, guideline-directed medical therapy is encouraged. Heart failure is a chronic condition, and patients often experience decompensation and poor health, even with medications. Hence, various medical devices and medical procedures have been developed to complement guideline-directed medical therapy and address heart failure etiologies. Other innovations recorded in the literature are regenerative medicine, genome editing, and precision medicine. This review also provides recommendations on future directions in the management of heart failure.

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