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Emerging Targeted Therapies in Heart Failure: Molecular Modulators, SGLT2 Inhibitors, and Novel Drug Delivery Systems

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ABSTRACT:

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide particularly among the elderly population. This review discusses novel targeted therapies to alter the progression of the disease rather than just reducing symptoms. Developments have been classified into three domains: molecular modulators, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and new drug delivery systems. Molecular therapies such as SERCA2a gene therapy, histone deacetylase (HDAC) inhibitors, and anti-fibrotic drugs such as TGF-β and galectin-3 inhibitors are aimed at central pathophysiological pathways such as calcium mishandling, epigenetic remodelling, and myocardial fibrosis. The first developed SGLT2 inhibitors were designed to treat diabetes and they have shown consistent cardiovascular benefits across all HF phenotypes through various mechanisms, e.g., augmented myocardial energetics and reduced inflammation. Advanced delivery systems like nanoparticles exosomes, hydrogels and CRISPR-Cas9 have the most precision, targeting and persistence of therapeutic effect. The review further highlights future directions, including multimodal therapeutic strategies, genomic-driven precision medicine, and artificial intelligence-assisted treatment planning. Despite these promising advancements, significant challenges remain, including issues related to clinical translation, accessibility, and long-term safety. This evolving landscape underscores a shift toward individualized and regenerative approaches in heart failure management.

1.Introduction

Heart failure (HF) is a complex clinical syndrome resulting from structural or functional impairment of ventricular filling or ejection of blood.(1) This condition affects more than 64 million individuals all over the world and it is among the leading cause of hospitalization among people who are above 65 years of age.(2) HF has a high potential to become prevalent since the number of people with risk factors like hypertension, obesity, diabetes, and coronary artery disease is on the rise, which may easily extend to its prevalence following the rise of the ageing population.(3) As proposed in the 2022 guidelines of the American Heart Association (together with the American College of Cardiology and the Heart Failure Society of America), heart failure (HF) is differentiated into several specific subgroups. This categorization is mostly defined by the left ventricular ejection fraction (LVEF) test, a very important factor that is evaluated by the use of echocardiograms. The LVEF measures the percentage of blood that is expelled from the left ventricle during each contraction of the heart. This systematic stratification is important due to the fact that it has important implication not only on prognosis of the condition but also on the therapeutic options that can be used.

HFrEF causes heart failure and is characterized by less than 40 percent ejection fraction of the left ventricles (LVEF). This category of heart failure characterizes an advanced level of systolic impairment, in other words, the ability of the heart to provide the required supply of blood to the body is grossly distorted and limited.

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Heart failure with a mildly reduced ejection fraction (HFmrEF) can be characterized as the left ventricular ejection fraction (LVEF) between 41 and 49 percent. Patients who fall into this "mid-range" category often have a mix of pathophysiological features, which can include characteristics of both systolic dysfunction and diastolic dysfunction.

Heart failure with preserved ejection fraction (HFpEF): LVEF ≥ 50%. In this systolic function is relatively preserved, but due to diastolic dysfunction – impaired ventricular relaxation and increased stiffness, – becomes primary. Such an LVEF-based categorization not only measures the extent of ventricular systolic dysfunction but also serves as a cornerstone for the direction of evidence-based management. For heart failure with reduced ejection fraction (HFrEF), there is a very large body of strong clinical trial evidence that supports the use of several distinct pharmacologic agents. These include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor–neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs). The use of these drugs is directed toward a specific set of important clinical outcomes, including lowering mortality rates, enhancing patients' symptoms, and avoiding the necessity for hospitalizations. In contrast, heart failure with preserved ejection fraction (HFpEF) is a much more significant therapeutic challenge to healthcare practitioners and patients. This disease is especially problematic because it is very common, notably in the elderly and in women, but there is a relative lack of treatments that have been scientifically demonstrated to improve survival. The treatment of HFpEF is for the most part symptomatic relief, with a strong emphasis on volume control strategies—such as the use of diuretics—and the treatment of comorbidities that are commonly associated with this disease, such as atrial fibrillation, hypertension, obesity, and diabetes. One of the key barriers to effective treatment of HFpEF is its heterogeneous nature. There are a variety of causative mechanisms underlying the syndrome, such as systemic inflammation present in obesity, stiffening of the myocardium through chronic high blood pressure, microvascular endothelial dysfunction and enhanced ventricular-vascular coupling. Consequently, patients with HFpEF can exhibit varying pathophysiological drivers of dominance, and therefore a unique uniform treatment approach is not feasible under this paradigm to benefit all patients with HFpEF.

Medical research has a newer tendency as the attention is gradually paid to the mechanism-specific treatments and interventions with a specific focus on unique phenotypes of different patients. These targeted strategies also include a host of diverse strategies such as anti-inflammatory therapy, anti-fibrotic therapy with the aim of reducing fibrosis, and a plethora of interventions targeting the therapy of metabolic dyfunction or micro - vascular disease. These novel precision medicine approaches hold enormous promise for overcoming the existing limitations with symptomatic therapy of health conditions, which may set the stage for the creation of disease-modifying treatments for heart failure with preserved ejection fraction, or HFpEF, in the near future.

Boolean logic connector (AND, OR).The final search strings included: "targeted therapy" AND "heart failure," “molecular modulators" OR "SERCA2a" OR "HDAC inhibitors," "SGLT2 inhibitors" AND "heart failure outcomes," and "nanoparticles" OR "gene therapy" OR "exosomes" OR "CRISPR."

2.Methodology

A structured, systematic literature search was conducted to find novel therapeutic strategies in heart failure (HF) in the HFrEF and HFpEF phenotypes. Three of the largest biomedical databases—PubMed, Scopus, and Web of Science—were chosen for their extensive coverage of clinical, translational, and preclinical research. The literature search was performed between January, 2015 to February, 2025, a timeline which spans the latest developments of molecular medicine, innovative approach of drug delivery and clinical use of sodium-glucose co-transporter 2 (SGLT2) inhibitors.

To achieve the best sensitivity and specificity, Mesh and free-text terms were used in advanced searches to obtain high quality and clinically relevant evidence. Only articles about original peer-reviewed studies, systematic reviews, meta-analyses, and the reports of clinical trials were selected, concentrated over new or emerging treatments in heart failure, including those relevant to reduced and preserved ejection fraction phenotypes. Studies were also required to provide mechanistic insight, translational relevance using preclinical models, or human data from phase 1–3 clinical trials, and non-English studies were excluded unless translated into English. Exclusion criteria included non-peer-reviewed publications, and conference abstracts with no full text,

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and articles that limited themselves to the traditional aspect of the treatment of heart failure without underlying mechanisms or innovations. Literature searches across the three databases were compiled in Zotero reference management software, with duplicates removed. Titles and abstracts were screened independently by two reviewers to assess eligibility, and full-text papers were appraised and disagreements resolved by consensus. Study design, the demographics of the population, the type of intervention, the mechanistic hypothesis, major results and findings of each study were extracted. A thematic synthesis technique was then employed to integrate data from preclinical and clinical studies, allowing cross-comparison of mechanistic research, translational models, and human trials to identify novel concepts with potential clinical relevance and place them into context.(4)(5)(6)

3.Classification of Studies

Therapeutic Classification

The qualified studies were grouped into three principal categories based on the nature and mechanism of the intervention: molecular modulators, SGLT2 inhibitors, and novel drug delivery systems. These classes of therapy all reflect the non-overlapping but complementary approaches that are striving to move the paradigm of heart failure treatment out of symptom management over into the mechanism-based, disease-modifying category of therapy.

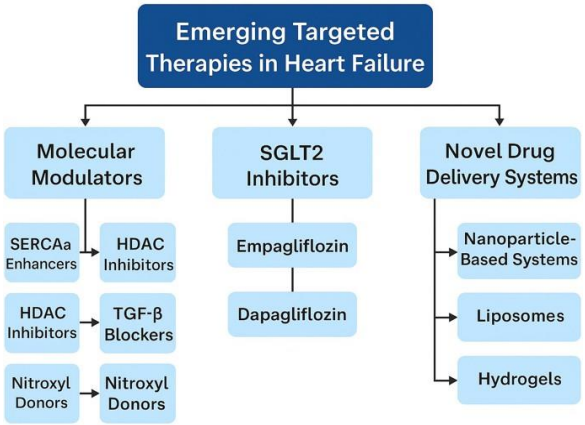

Figure 1: Overview of Novel Targeted Therapeutic Approaches in Heart Failure

Molecular modulators - These are medications/genetic therapies that target the intracellular signalling pathways that are pivotal to cardiac functioning. Important targets are also calcium cycling proteins, which are critical to effective myocardial relaxation and contraction, including sarcoplasmic reticulum ca^{2+} ATPase 2a (SERCA 2a). Gene therapy with SERCA2a has been considered to correct calcium homeostasis in failing myocardium in order to enhance the contractile performance. The other example is the histone deacetylase (HDAC) inhibitor, making adaptations in the gene expression pattern to reduce cardiac expression patterns of myocardial fibrosis and pathological remodelling. Taken together, all these methods are designed to revert dysfunctional signalling pathways as opposed to symptomatic reduction.

SGLT2 inhibitors One of the most effective therapeutic classes in recent heart failure studies, sodium-glucose cotransporter-2 (SGLT2) inhibitors were originally developed as glucose-lowering compounds used in management of patients with type 2 diabetes mellitus. Their pleiotropic effects have been established to be beneficial on the outcomes of diabetic and non-diabetic groups of HF, where the products have been shown to reduce rates of hospitalization, increase functional capacity, improvement in quality of life, and beneficial effects at the level of the loading condition of the ventricle and systemic hemodynamics. The exact mechanisms are still uncertain, although suggested mechanisms include osmotic diuresis, enhanced myocardial energetics, dampening of inflammatory signalling, and arrested adverse ventricular remodelling.

New drug delivery systems are being developed to improve therapeutic accuracy and persistence at reduced off-target effects. These are nanoparticle-based targeted drug delivery vehicles, which can deliver high doses of drugs to the cardiac tissue; long-term and tissue-specific expression of therapeutic proteins, delivered by gene therapy vectors (viral and non-viral); small vesicle-based transport systems, exosomes, which take advantage of nature-mediated vesicle communication pathways; and CRISPR/Cas genome editing technologies, which have the promise of fundamentally correct future-inducing mutations in inherited cardiomyopathies. This may allow individual, etiology-specific, and potentially curative treatments directly targeting the underlying molecular or genetic errors that are causing the development of HF.

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3.1 serca2a Gene Therapy

The tight control of intracellular calcium cycling is of paramount importance to the cardiac mechanics. Every beat relies on tightly controlled cycles of calcium-release and calcium-re-take-up by cardiomyocytes, a cycle on which both systolic contraction and diastolic relaxation can be based. A central component of this machinery is the sarcoplasmic/endoplasmic reticulum calcium ATPase isoform 2a (SERCA2a), an ATP-activated calcium pump of the sarcoplasmic reticulum (SR) membrane. Through active transport of calcium from the cytosol to the SR during diastole, SERCA2a not only allows the ventricle to relax rapidly, but also ensures adequate storage of calcium for the next contraction.

In the failing heart, SERCA2a activity and expression are always diminished. Such abnormality results in delayed cytosolic calcium increase during diastole, residual ventricular relaxation, reduced SR calcium content, and thus reduced contractile force during systole. Such abnormalities of calcium handling result in diastolic dysfunction, systolic dysfunction, and arrhythmogenesis caused by delayed clearance of calcium that can result in spontaneous SR calcium release events that predispose to ventricular arrhythmias.

Due to this pathogenic critical role, restoration of SERCA2a function emerged as a very attractive therapeutic strategy in the early 2000s. Preclinical experience in animal models of heart failure had established that gene transfer of SERCA2a would correct calcium cycling, increase myocardial contractility, reverse pathological remodeling, and reduce arrhythmic susceptibility. The most widely used delivery platform in clinical trials has been adeno-associated virus serotype 1 (AAV1), which was used for its relatively innocuous immune profile as well as for its cardiac tissue tropism.

The CUPID (Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) trial was the initial large-scale clinical application of this technique:

CUPID 1 (Phase 1/2a) – In patients with advanced HFrEF, this trial showed that a single intracoronary dose of AAV1/SERCA2a was safe and well tolerated. Importantly, exploratory endpoints showed potential clinical benefit in the form of improved New York Heart Association (NYHA) functional class, decrease in NT-proBNP levels, and positive trends in LVEF and time to cardiovascular events. These results created a lot of excitement to test in larger in confirmatory trials.

CUPID 2 (Phase 2b) – A double-blind, randomized, placebo-controlled study intended to measure definitively for efficacy, this trial failed to reach its initial endpoint to reduce recurrent HF hospitalization or all-cause death. There were no statistically significant differences in high-level secondary endpoints, and accordingly, it was concluded that, in the form in which it was under investigation, SERCA2a gene therapy was not associated with an actionable clinical benefit in this patient population.

Failure of the CUPID 2 trial is believed to be caused by a number of factors which are interrelated. The possibility of insufficient intracoronary delivery resulting in poor myocardial transduction, especially in severely scarred/fibrotic tissue might have occurred. There was a limitation in the use of AAV1 vectors because this serotype, although non-pathogenic, shows only moderate cardiac tropism relative to more recent genetically modified capsids. The selection of patients could have been a variable also, as most of the participants were in late disease state with severe remodeling and little salvageable tissue. Also, inhibitory humoral responses against AAV1 probably hindered efficient delivery of the gene in a fraction of individuals. Although this has limited SERCA2a as a therapeutic target, it remains a promising area of investigation and recent research efforts were geared towards addressing these obstacles. These progress developments are as follows: third-generation AAV capsids have been developed with improved cardiac tropism and transduction capacity, immune evasion approaches that include capsid modifications or temporary immune suppression, and improved dosing schedules that maintain the highest level of efficacy within the most appropriate realm of safety. This would be further enhanced by earlier intervention in the disease course especially in patients that exhibit defects in calcium-cycling that could be demonstrated yet fibrosis is minimal. Furthermore, combinatoric strategies that combine SERCA2a gene therapy with antifibrotic medicines, metabolic correction medicines, or mechanical unloading, are under study to establish a better myocardial environment. Provided that these innovations are effective, SERCA2a-based therapy may still live up to its promise as a mechanism-based, disease-

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modifying therapy in heart failure, potentially in phenotypes with severe defects in calcium handling.

3.2 HDAC Inhibitors

Histone deacetylases (HDACs) manage gene expression, by chromatin remodelling. In HF, hypertrophy and fibrogenesis are stimulated by HDAC overexpression. Maladaptive epigenetic profiles are corrected by HDAC inhibitors including trichostatin A and vorinostat and thereby limiting myocardial damage in pre-clinical models.(7) The agents provide a distinctive opportunity to regulate transcription without sequence changes in the DNA.

It is also claimed that HDAC inhibition displays immunomodulatory activities, including reduction of pro-inflammatory cytokines and fibroblast activation.(8) Nevertheless, toxicity profile and off-target toxicity are still a concern, and future trials require improved isoform-specific HDAC inhibitors.

3.3 TGF-beta and Galectin-3 Blockers

The stiffening of ventricles in HFpEF patients is also majorly due to cardiac fibrosis. TGF-beta is an inhibitor of fibroblast activation and extracellular deposition, and through these mechanisms reversing diastolic dysfunction is a possible outcome.(9) Likewise, galectin-3 antagonists decrease the pro-fibrotic signaling and have been found to be of benefit in animal models.(10) Although not yet in late-phase trials, these agents represent precision anti-fibrotic therapies that directly counteract one of HF's most elusive targets—ventricular stiffness and remodelling.

4 SGLT2 Inhibitors

The reclassification of SGLT2 inhibitors from anti-diabetic drugs to heart failure drugs is one of the most significant breakthroughs in cardiovascular therapeutics in the past decade. These agents have pleiotropic effects beyond their effects on glucose metabolism.(11)

4.1 Mechanism of action

The inhibition of SGLT 2 by inhibitors of the SGLT 2 drug type blocks glucose reabsorption in the proximal renal tubules leading to glycosuria and natriuresis.(12) This action, originally targeted at treating type 2 diabetes mellitus, has surprisingly provided large cardiovascular advantages, especially against heart failure (HF). The groundbreaking finding that these effects translate to patients without diabetes has revolutionized the treatment paradigm and resulted in the universal adoption of SGLT2 inhibitors into global HF guidelines. The cardiovascular benefits of SGLT2 inhibitors are heterogeneous and rooted in hemodynamic as well as non-hemodynamic mechanisms.

Osmotic diuresis and natriuresis by generating glucosuria SGLT2 inhibitors create osmotic gradient conducive to water excretion but intravascular and interstitial volume are concomitantly reduced due to natriuresis. The combined effect decreases preload, reduces pulmonary congestion, and enhances right and left ventricular filling pressures without attendant neurohormonal activation that is frequently associated with loop diuretics.

Blood pressure lowering- chronic blood pressure lowering is realized through reduction of arterial stiffness, plasma volume, and improvements in endothelial function. These act to reduce afterload and increase stroke volume and overall efficiency of the heart, but without tachycardia reflex.

Improved myocardial energetics – inhibition of SGLT2 seems to divert cardiac substrate utilization towards ketone bodies, which have a higher ATP yield per unit of oxygen consumed than glucose or fatty acids. Such metabolic reprogramming can enhance myocardial energy efficiency, especially useful in the energy-deprived failing heart.(13)

Anti-inflammatory and antioxidant effects- Various studies have shown a significant decrease in pro-inflammatory cytokine such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) and an oxidative stress biomarker. All these actions can potentially limit pathological myocardial remodeling and decelerate the advancement of HF.(14)

Autonomic modulation - Emerging evidence has shown that SGLT2 inhibitors abate sympathetic nervous activity and heighten vascular compliance, in addition to leading to superior hemodynamics and organ perfusion. Such interventions are particularly useful in the HF pathophysiologic setting in which the neuro hormonal activation, chronic volume overload, endothelial dysfunction and metabolic inefficiency contribute to exacerbating the disease process. SGLT2 inhibitors can simultaneously block several pathogenic pathways thus

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alleviate symptoms and have disease-modifying effects.

Large-scale randomized controlled trials (including DAPA-HF (dapagliflozin), EMPEROR-Reduced (empagliflozin) and EMPEROR-Preserved) have demonstrated substantial reductions in HF hospitalization and have improved quality of life without relying on baseline diabetes status. This double-barreled use across HFrEF and HFpEF renders SGLT2 inhibitors one of the few therapeutic classes with widespread use across the HF spectrum.

Following these consistent benefits, SGLT2 inhibitors are now solidly established as first-line therapy for HFrEF and as an evidence-based treatment in HFpEF, being one of the most significant therapeutic advances in the treatment of heart failure in the past decade.

4.2 Landmark Clinical Trials

The effectiveness of SGLT2 inhibitors in heart failures (HF) has been proved by several large randomized controlled trials (RCTs). In the DAPA-HF trial (2019), dapagliflozin bypassed the composite of cardiovascular death and HF hospitalization in patients with HFrEF (as well as in those without diabetes).(15) Likewise, a study of the EMPEROR-Reduced (2020) confirmed that empagliflozin resulted in a 25% decrease in HF events and renal deterioration was less.(16) In patients with HFpEF, dapagliflozin has been shown to reduce symptoms and improve functional outcomes in the DELIVER trial (2022) to a previously treatment-refractory subtype,(17) as well as the first study to show benefits in patients with EF =50%(18) in the EMPEROR-Preserved trial (2021). A follow-on meta-analysis confirmed these results and a relative risk of hospitalization reduction across all EF groups of 20 30 per cent.(19) Taken together, this body of evidence has placed SGLT2 inhibitors in a class I recommendation in the most current HF management guidelines.(20)

5. Technical Drug Delivery Systems

Delivery of the therapeutic agent to the heart with precision, efficacy, and permanency and reduced systemic toxicity remains one of the key challenges in heart failure pharmacotherapy. This is changing with emerging technologies, i.e., nanoparticle, exosomes, hydrogel, and CRISPR-based systems, which redefine this field.

5.1 Nanoparticles (NPs)

Nanoparticles (NPs) of functionalized dimension between 1 and 100 nm are designed and engineered to transport drugs by selectively delivering therapeutics to the damaged myocardial tissue where local drug concentrations amplified can be at minimal systemic levels of side effects.(21) Some NP platforms have been explored, which include polymeric NPs that encapsulate both hydrophilic and hydrophobic drugs, as well as lipid-based NPs (liposomes that can carry small-molecule inhibitors or nucleic acids (e.g., miRNAs and siRNAs) and ligand-functionalized NPs (e.g., with antibodies or peptides) to target receptors overexpressed on ischemic myocardium.(22) Preclinical results show that statin-loaded or VEGF-loaded nanoparticles facilitate infarct repair and angiogenesis in the myocardium; in one mouse model, VEGF-loaded NPs increased left ventricular ejection fraction by 25% relative to controls.(23) Although experimental outcomes are encouraging, translation to the clinical setting is still ongoing, and regulatory, production, and immune clearance barriers have to be solved before large-scale implementation.

5.2 Exosomes

Exosomes are nano-vesicles (30–150 nm) naturally secreted by cells that carry bioactive contents such as mRNAs, microRNAs, lipids, and proteins.(24) They replicate many of the therapeutic effects of their parent cells particularly mesenchymal stem cells (MSCs) while avoiding the risks associated with whole-cell therapy.(25) Exosomes Produced by induced pluripotent stem cells (iPSCs) or cardiac progenitor cells The application of exosomes produced by induced pluripotent stem cells (iPSCs) or cardiac progenitor cells, have demonstrated pro- angiogenic effects,reduce apoptosis and improving fibrosis scores in heart failure models.(26) In addition to their native functions, engineered exosome-based delivery systems may as well be used to transport synthetic therapeutics, SIRNAs, or gene-editing factors.(27) Their advantages include high biocompatibility, minimal immunogenicity, the ability to cross biological barriers, and an intrinsic homing capacity to damaged tissue. With these properties, engineered exosomes are anticipated to emerge over the next decade as a mainstream delivery platform for gene therapy in cardiovascular disease.

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5.3 Hydrogels

The scaffolds with three-dimensional and high-water content (hydrogels) can be used to enmesh hydroxyapatite, drugs, or stem cells, with drugs or stem cells released in a controlled and sustained fashion.(28) They have commonly been used to deliver angiogenic factors mediators such as VEGF or FGF to local areas, coated with B-blockers or anti-inflammatory agents to act in specific areas of the heart, and allowed the delivery of cardiac patches or stem cells. It has been shown by preclinical tests that the in vivo hydrogel-based delivery systems can enhance cardiac regeneration and boost the therapeutic retention.(29)(30) In addition, there are stimuli-responsive advanced hydrogels that commence discharging their cargo in reaction to environmental modifications, such as pH or temperature, which supports smart, wound-specific delivery of drugs.

5.4 Genes CRISPR-Cas9

CRISPR/Cas9 is a disruptive technology that allows selective editing of genomic material and it is being investigated as a potential modality in cardiology. Possible modalities are correction of hereditary cardiomyopathies (such as LMNA or MYH7 mutations), induction of cardiomyoprotective proteins (such as SERCA2a) and inhibition of pro-fibrotic or pro-arrhythmic genes.(31) Recently, a landmark study showed that one injection of CRISPR/Cas9 against a mutation in a dystrophin gene led to the repair of heart function close to normal in mouse models of Duchenne muscular dystrophy.(32) Although this is a promising step, the issues associated with off-target activities, ethical positions, and safety over a long period of time have to be overcome before moving CRISPR-based therapies to extensive clinical practice.

6. Future directions

The heart failure treatment arena is fast-growing. With the advancement in comprehending molecular biology, genomic, and tissue engineering, future treatment will probably be on personalized, multimodal, regenerative-based medicine.

6.1 Combination Therapies

The combination of various treatment strategies can be identified as one of the hopeful methods of managing heart failure. The combination of SGLT2 inhibitors with angiotensin receptor neprilysin inhibitors (ARNIs, e.g., sacubitril/valsartan), beta-blockers and mineralocorticoid receptor antagonists (MRAs) has shown additive effects in enhancing left ventricular ejection fraction, NT-proBNP levels and hospitalizations.(33)(34) As an example, in the EMPEROR-Reduced trial, the response observed in patients treated with both empagliflozin and an ARNI was synergistic in terms of a reduced adverse clinical outcome. Moving to the future, therapeutic regimens are likely to include molecular modulators, such as HDAC or TGF-ins inhibitors, in combination with the conventional drugs, thus killing two birds with one stone, by relieving symptoms and targeting underlying pathophysiology.

6.2 Personalized/Genomic Medicine

Standard therapies do not affect every patient with heart failure in the same way. With advances in genomic profiling, transcriptomics, proteomics, and metabolomics, the development of precision medicine is now starting to open new avenues of patient-personalized selection of treatment and development of personalized therapies specific to clinical need.(35)(36) As another example, some varieties of SGLT2 inhibitors can prove to be more effective in individuals with particular genetic polymorphisms,(37) whereas gene therapies including CRISPR-based editing or genetic regulation of SERCA2a can be tailored in patients with particular genetic mutation.(38) In addition, pharmacogenomics has the promise of significantly decreasing adverse drug responses that continue to mark great hindrance towards optimal therapeutical management of heart failure.

4.3Artificial Intelligence (AI)

Machine learning and AI-based systems are increasingly being integrated into electronic health records (EHRs) for real-time risk prediction, as well as into imaging analysis for tasks such as automated strain or ejection fraction calculations. They are being put to work even in therapeutic choice algorithms.(39) Machine learning models will allow stratifying patients based on the probability of their response to SGLT2 inhibitors or the risk of decompensation, taking advantage of large amounts of data. Furthermore, AI holds promise in the near future for designing customized drug-delivery regimens tailored to biomarker profiles and disease stage.(40)

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6.4 Stem Cells and regenerative therapies

The regenerative capacity of cardiac tissue is limited, though recent research in induced pluripotent stem cells (iPSCs), cardiac progenitor cells (CPCs), and bioengineered heart patches hold promise of restoring cardiac function by reversing scar tissue and in chronic heart failure (HF).(41)(42) Additionally, exosomes derived from stem cells may overcome the complexities associated with whole-cell therapy while preserving regenerative effects [49]. Clinical trials will likely be conducted in the future in an attempt to understand whether these biologics alone or together with delivery platforms like hydrogel or nanoparticles can be used to regenerate viable myocardium.

7. Limits

Although most of these emerging therapies have encouraging results, they have significant limitations as shown below:

7.1 Expensive and Availability

Gene therapy and CRISPR, as well as nanoparticles, are costly to manufacture and need to be done using specific infrastructure. In the low- and middle-income countries (LMICs), cost-effectiveness will remain a significant barrier.(43)

7.2 Translational Gaps

Several therapies have demonstrated efficacy in preclinical animal models, but human trials have not yet replicated these outcomes.(44)(45) The CUPID-2 failure is an indication to us that preclinical success does not mean clinical efficacy.

7.3 Long-term Safety

The long-term risks of gene editing, HDAC inhibitors, or engineered exosomes remain unknown.(46) There is concern about immune activation, tumorigenicity, and off-target genomic effects.

7.4 Disease heterogeneity

HFpEF encompasses a heterogeneous set of pathophysiology, ranging from obesity and hypertension to aging and amyloidosis—making a single therapy insufficient.(47)

8. Conclusion

The management of heart failure, or HF, is now on the verge of a revolutionary new era that is dominated by significant breakthroughs in areas such as molecular targeting, cellular engineering, and intelligent drug delivery systems. The hitherto conventional approach, which has so far relied on a one-size-fits-all approach, is increasingly being challenged by a more sophisticated precision-based approach, strongly rooted in the principles of systems biology. New molecular modulators such as SERCA2a enhancers, HDAC inhibitors, TGF-β blockers, and gene therapy hold the exciting promise to address the underlying pathophysiology of heart failure at its very roots. Meanwhile, SGLT2 inhibitors have already made significant strides in transforming heart failure treatment guidelines since they were shown to be effective for diabetic as well as non-diabetic patients across the whole spectrum of ejection fraction. Parallel to these developments, next-generation drug delivery systems, which constitute a spectrum of technologies such as nanoparticles, liposomes, exosomes, hydrogels, and CRISPR-based systems, have the potential to enhance therapeutic specificity while, simultaneously, reducing systemic toxicity, which is a concern with traditional treatments. It is, however, essential that these new technologies are rigorously validated through large randomized controlled trials to assure that they are not only effective but also made cost-effective by cost-reduction strategies, and standardized within existing regulatory protocols to allow consistent clinical use in varied healthcare settings. As these cutting-edge precision therapies continue to move from the laboratory bench to actual bedside clinical use, the future for millions of patients with heart failure can potentially witness a radical shift from merely palliating symptoms to actually modifying disease, and in some cases, even the possibility of an actual cure.

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