ADVANCEMENTS IN HEART FAILURE MANAGEMENT: FROM NEUROHORMONAL MODULATION TO EMERGING REGENERATIVE THERAPIES

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Research objective

Heart failure (HF) is a complex clinical syndrome characterized by the heart’s inability to pump sufficient blood to meet the metabolic demands of the body. It is a final common pathway for many cardiovascular diseases and remains one of the leading causes of hospitalization, morbidity, and mortality worldwide. The primary goal of this research is to analyze the evolution of heart failure management, focusing on the progression from traditional neurohormonal modulation to advanced regenerative therapies and personalized medicine strategies. The multifactorial pathophysiology of HF involves not only systolic or diastolic dysfunction but also neurohormonal dysregulation, inflammatory processes, oxidative stress, mitochondrial dysfunction, and extracellular matrix remodeling. Traditionally, HF has been classified based on left ventricular ejection fraction (LVEF) into HF with reduced EF (HFrEF), preserved EF (HFpEF), and mid-range EF (HFmrEF). However, evolving evidence suggests a need for more phenotype-specific treatment approaches that incorporate biomarkers, imaging data, and genetic profiling.

Introduction

The cornerstone of HFrEF treatment has historically involved neurohormonal antagonism. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) have demonstrated significant reductions in mortality and hospitalization in large randomized controlled trials. More recently, angiotensin receptor-neprilysin inhibitors (ARNIs), particularly sacubitril/valsartan, have revolutionized the therapeutic landscape by providing superior outcomes compared to traditional RAAS inhibition, as demonstrated in the PARADIGM-HF trial. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, initially developed for diabetes management, have now emerged as a class of drugs with robust cardiovascular and renal benefits in both diabetic and non-diabetic HF patients. DAPA-HF and EMPEROR-Reduced trials have confirmed their efficacy in reducing HF-related hospitalizations and cardiovascular death. These pharmacologic advancements are often complemented by device-based therapies. Cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICDs) are standard in patients with specific conduction abnormalities and at high risk of sudden cardiac death. Hemodynamic monitoring devices, such as CardioMEMS, enable early detection of volume overload and preemptive management of decompensation.

Materials and Methods

In HFpEF, where therapeutic options have traditionally been limited, recent trials like EMPEROR-Preserved and DELIVER have shown that SGLT2 inhibitors also confer meaningful benefits, shifting the treatment paradigm in this previously untreatable phenotype. Ongoing investigations into the use of mineralocorticoid receptor antagonists, ARNIs, and anti-fibrotic

agents in HFpEF patients offer hope for improved outcomes. Biomarkers such as natriuretic peptides (BNP, NT-proBNP), troponins, galectin-3, ST2, and growth differentiation factor-15 (GDF-15) are increasingly used for diagnosis, risk stratification, and therapeutic monitoring. Novel biomarkers including circulating microRNAs, exosomes, and proteomic signatures are under active exploration for their potential to refine phenotyping and guide individualized therapy. Advanced imaging techniques such as speckle-tracking echocardiography, cardiac MRI with late gadolinium enhancement, and nuclear imaging for myocardial metabolism provide valuable insights into myocardial structure and function, guiding therapeutic decisions.

Results

Regenerative therapies represent a frontier in HF treatment, aiming to restore myocardial integrity and function. Stem cell-based approaches, including mesenchymal stem cells (MSCs), cardiac progenitor cells, and induced pluripotent stem cells (iPSCs), have demonstrated variable results in clinical trials, often limited by delivery efficiency, cell survival, and host immune response. Bioengineered tissues, gene editing techniques like CRISPR/Cas9, and extracellular vesicle therapies are being actively studied for their potential to reverse or mitigate myocardial injury. Gene therapy targeting SERCA2a, adenylyl cyclase, and nitric oxide pathways has shown promise in preclinical models and early-phase trials. Moreover, tissue engineering with decellularized scaffolds and 3D bioprinting of cardiac patches represents an innovative approach toward myocardial regeneration.

The integration of artificial intelligence (AI) and machine learning into HF care has enabled the development of predictive models for readmission risk, therapy optimization, and phenotypic classification. Digital health tools, including wearable devices, remote patient monitoring, and telemedicine, have become essential components of chronic HF management, particularly in the post-COVID era. Multidisciplinary HF clinics involving cardiologists, pharmacists, nurses, nutritionists, and palliative care specialists have demonstrated significant benefits in patient adherence, quality of life, and survival.

Conclusion

Despite these advances, challenges remain in addressing disparities in access to care, medication adherence, and disease awareness, particularly in low- and middle-income countries. Socioeconomic factors, health literacy, and comorbidities like chronic kidney disease, diabetes, anemia, and frailty complicate management strategies. Moreover, sex-specific differences in HF presentation and response to therapy are increasingly recognized, necessitating inclusive research and sex-aware clinical decision-making.

In conclusion, heart failure management has transitioned from symptomatic relief to a comprehensive, mechanistically targeted, and increasingly personalized approach. The future of HF care lies in integrating molecular insights, advanced therapeutics, and patient-centered care models to improve outcomes and quality of life for this growing patient population. Continued research, innovation, and equitable implementation of evidence-based practices are crucial for transforming the HF treatment landscape in the coming decades.

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