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THE IMPORTANCE OF CARDIOTONIC DRUGS IN MEDICAL PRACTICE, THE RANGE OF APPLICATIONS AND THE ADVANTAGES OF THEIR USE

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Abstract: There are multiple evidence-based drug treatments for chronic heart failure (HF), both disease-modifying agents and those for symptom control. The majority of the evidence base supports drugs used in HF with reduced left ventricular ejection fraction. The mainstay of disease modification involves manipulation of neurohormonal activation that occurs in HF. In addition to established angiotensin-converting enzyme inhibitors, beta blockers and mineralocorticoid receptor antagonists (MRAs), newer agents are now available such as the angiotensin receptor neprilysin inhibitors. Achieving the optimal drug regimen is complex and best performed by a specialist heart failure team. We aim to provide a comprehensive overview of contemporary drug therapies in chronic heart failure, as well as practical guidance for their use. Treatment of patients with difficult comorbidities, including hypotension and chronic kidney disease (CKD), where a comprehensive knowledge of medication management is crucial, is the emphasis, and there are several current trials evaluating the advantages of novel treatments for heart failure, like intravenous iron. Predictive models for early intervention, risk assessment, and individualized therapy recommendations have also been made possible by the integration of AI and machine learning in the management of heart failure. By focusing on the disease's underlying mechanisms, these novel treatments for heart failure have the potential to completely transform the sector, as this narrative review highlights. By investigating these cutting-edge strategies, we seek to offer a thorough understanding of the changing paradigm of heart failure care, encouraging optimism in both patients and physicians.

Key words: heart failure, cardiac care, thorough study, new treatments, developments, management.

Introduction. Typical symptoms of heart failure (HF), a clinical syndrome, include peripheral oedema, fatigue, dyspnea, and elevated jugular vein pressure. It is brought on by a number of illnesses, such as primary cardiomyopathies, valvular heart disease, hypertension, and ischemic heart disease (IHD), all of which produce structural and/or functional abnormalities in the heart. In the western world, ischemic heart disease is the most prevalent cause. Heart failure is common, the Rotterdam Study reported a prevalence of 0.9% in subjects aged 55–64 years, rising to 17.4% in those aged ≥85.3 The lifetime risk for 55-year-olds was 33% for men and 29% for women. Heart failure is responsible for 1–2% of western healthcare systems budgets and inevitably will rise with an ageing population [1-5]. The bulk of cost relates to frequent and lengthy hospitalisations. While prognosis has improved, it still remains poor – recent UK data show in-hospital mortality rates of 8.9%, median length of stay at 9 days and of those surviving to discharge 26.7% die within a year. The mainstay of treatment for HF is drug therapy. By promptly identifying patients with HF and commencing evidence-based therapies it is possible to markedly improve morbidity and mortality. Patients with HF have typically been grouped into those with preserved or reduced left ventricular (LV) systolic function. Recent guidelines have further divided patients according to LV ejection fraction (EF, LVEF): HF with reduced EF (HFrEF) – EF <40%, HF with preserved EF (HFpEF)–EF ≥50%, and the relatively new term HF with mid-range

EF (HFmrEF) – EF 40–9% [6-9]. The presence of symptoms, with or without signs of heart failure, is the unifying factor for the diagnosis of HFpEF. Other characteristics that are necessary to make the diagnosis include elevated natriuretic peptides, relevant structural heart disease (e.g., left ventricular hypertrophy), and/or markers of diastolic dysfunction. Recent guidelines have further divided patients according to LV ejection fraction (EF, LVEF): HF with reduced EF (HFrEF) – EF <40%, HF with preserved EF (HFpEF) ≥50%, and the relatively new term HF with mid-range EF (HFmrEF) – EF 40–9%.6 The evidence that drug therapy improves prognosis (markedly reduced hospitalization and mortality) is overwhelming [10-13]. However, in practice, many of the medications used to treat HFpEF (and HFmrEF) are also used to treat symptoms and modify risk factors for HF, such as hypertension. The inclusion of HFmrEF is intended to stimulate research for this group, in order to identify the underlying pathophysiology as well as effective treatment options for this group, but it may actually create a degree of clinical uncertainty. In contrast, there is currently no evidence that medications improve outcomes for patients with HFpEF (or HFmrEF). Notably, all HF patients are evaluated for additional evidence-based treatments, such as cardiac rehabilitation and device therapy (implantable cardioverter defibrillators, cardiac resynchronization therapy), in addition to medication therapy [14-17]. Identifying topics that require further research can be a useful tool in guiding future research endeavors and promoting a culture of ongoing innovation. Each developing therapy will be subjected to a rigorous evaluation, evaluating its inherent limitations and merits. A thorough review of these therapeutic approaches will provide physicians and researchers with valuable insights to facilitate informed decision-making on their integration into clinical practice. The narrative review will conclude by suggesting potential avenues for future study and advancement in heart failure management [18-20].

The main purpose of this analytical manuscript is to provide a brief overview of cardiotonic drugs based on scientific research on their importance in medical practice, the range of applications and the benefits of their use.

Recognizing heart failure. A complex and incapacitating clinical illness, heart failure is defined by the heart's incapacity to adequately pump blood to meet the body's metabolic needs. It is a major global health issue that affects millions of people and puts a burden on healthcare systems all around the world. The goal of this in-depth essay is to give a thorough overview of heart failure, covering its definition, pathophysiology, epidemiology, and classification. It will also explore the disease's multifaceted character and difficulties. Congestive heart failure, another name for heart failure, is a complicated clinical illness characterized by the heart's impaired capacity to pump blood effectively, which leaves the body without enough oxygen and circulation to meet its metabolic needs. It is a syndrome that results from a number of cardiovascular and non-cardiovascular factors rather than a single disease entity [1-4].

The study of heart failure epidemiology. Millions of individuals throughout the world suffer from heart failure, a widespread health issue. Ageing populations, increased survival after heart attacks, and a growing load of risk factors like obesity, diabetes, and hypertension are all contributing factors to its rising prevalence. An estimated 6.2 million persons in the United States who were 20 years of age or older suffered from heart failure in 2019. Heart failure is linked to a significant burden of illness and mortality. The severity, underlying cause, and availability of medical care all affect the prognosis. Advanced heart failure can have a five-year mortality rate of over 50%, whereas the one-year mortality rate after diagnosis can be between 20% and 30% [9-12]. Furthermore, the economic impact of heart failure is substantial, with recurrent hospitalizations, costly interventions, and long-term management contributing to a substantial financial strain on healthcare systems. In 2012, the estimated direct and indirect costs of heart failure in the United States alone exceeded $30 billion. Heart failure is also a leading cause of hospitalization among older adults, affecting healthcare systems financially [14-18].

Newer agents with prognostic benefit. Elevated heart rate has consistently been associated with worse outcome in patients with HF. Beta blockers are not always tolerated by patients with HFrEF, nor are they always administered at doses sufficient to lower resting heart rate. Ivabradine is an If (‘funny’ channel) inhibitor acting on the sinoatrial node to slow heart rate (therefore only useful in sinus

rhythm). The SHIFT study showed benefit on the combined endpoint of cardiovascular death and HF hospitalisation when ivabradine was added to maximum tolerated doses of beta blockers as well as ACEi/ARB and MRA (mainly due to reduction in HF admissions) [5-9]. Following beta blocker optimization, its usage for patients with HFrEF and resting heart rates ≥75 bpm was approved by the National Institute for Health and Care Excellence (NICE). Ivabradine is generally well accepted, has no negative effects on blood pressure, and is linked to better quality of life. The first member of the novel class of medications known as angiotensin receptor neprilysin inhibitors (ARNIs) is a combination of valsartan (ARB) and sacubitril (neprilysin inhibitor). The latter enhances the positive counter-regulatory effects of natriuretic peptides and other vasodilatory peptides. In individuals with HFrEF, the PARADIGM-HF clinical study demonstrated that sacubitril/valsartan was more effective than enalapril at lowering the risk of cardiovascular death and HF-related hospitalization. Because sacubitril/valsartan significantly improved survival, the experiment was terminated early [7-12]. NICE released the following criteria for the use of sacubitril/valsartan in HFrEF: LVEF ≤35% established on stable dose of ACEi or ARB, New York Heart Association class II–IV. For individuals with HFrEF who continue to experience symptoms after receiving treatment with ACEi, beta blockers, and MRA, the European Society of Cardiology (ESC) recommendations propose sacubitril/valsartan. 6. Before starting sacubitril/valsartan, ACEi must be stopped for at least 36 hours if it has been the standard of therapy. Renal function is monitored in the same way as ACEi and ARB [14-18].

Current state of treatment. Over the past few decades, there has been a considerable evolution in the management of heart failure, with an emphasis on symptom relief, quality of life enhancement, hospitalization reduction, and survival extension. With a primary distinction between HFrEF and HFpEF, treatment approaches are customized based on the type and stage of heart failure. This section will examine current heart failure management techniques and treatments, such as medication, device-based therapy, and lifestyle changes. It will also draw attention to the shortcomings of the available therapies and stress the continuous need for innovation in the treatment of heart failure [7-10].

Pharmacological Interventions: ACE inhibitors have been a mainstay in the treatment of heart failure by reducing the production of *angiotensin II,* a powerful vasoconstrictor, and aldosterone, which results in vasodilation and a decrease in sodium and water retention. Important medications in this class include *enalapril, lisinopril,* and *ramipril;* the landmark consensus trial showed that enalapril significantly reduced mortality in patients with severe heart failure; ARBs, like losartan and valsartan, provide an alternative for patients who are intolerant to ACE inhibitors; they block the action of angiotensin II at the receptor level and have been shown to be effective in lowering morbidity and mortality in heart failure patients; beta-blockers, such as carvedilol, metoprolol, and bisoprolol, have become an important therapeutic option for HFrEF [11-15]. The *CIBIS-II* trial showed that *bisoprolol* was effective in lowering mortality in patients with HFrEF. *Mineralocorticoid receptor antagonists (MRAs)*, like *spironolactone* and *eplerenone*, target aldosterone receptors, counteracting their sodium and water-retaining effects. The RALES trial showed that spironolactone was beneficial in lowering mortality in patients with severe HFrEF. *Sacubitril/valsartan*, a combination of a *neprilysin inhibitor* (sacubitril) and an ARB (valsartan), is a novel treatment for HFrEF; it increases natriuretic peptide levels while blocking the negative effects of angiotensin II. The PARADIGM-HF trial showed that sacubitril/valsartan was superior to enalapril in lowering cardiovascular mortality and heart failure hospitalizations [15-20].

A meta-analysis of randomised controlled trials involving loop or thiazide diuretics showed improvements in exercise capacity, risk of disease progression, and risk of death, although the latter was based on data from small trials. More recently, a retrospective study demonstrated a reduction in hospital and 1-year mortality with more intensive diuretic use (as well as improved use of evidence-based therapies via a multidisciplinary team approach). When it comes to the choice of oral loop diuretics, furosemide has greater variability in absorption, but no study has found a significant difference in outcomes between it and bumetanide [3,4,6]. A period of intravenous diuretic therapy is generally warranted when patients present with decompensated HF, i.e., marked fluid excess; many of these patients have chronic kidney disease (CKD), and the decompensation is often associated with

worsening renal function or acute kidney injury (AKI); achieving euvolaemia is fundamental, and many patients require high doses of intravenous loop diuretics, as well as for some additional thiazide diuretics and MRA (progressive nephron blockade). It is important to keep in mind that, generally, the deterioration in renal function has been caused by congestion rather than the diuretics; data, though typically observational, indicate that the adverse prognosis is more affected by the continued presence of oedema than by a decline in renal function during hospitalization [11-15].

Discussion. Heart failure is a significant and growing global health issue that affects millions of people worldwide. It is a complex syndrome that results from a variety of etiologies, including ischemic heart disease, hypertension, valvular abnormalities, and cardiomyopathies. Heart failure is characterized by the heart's inability to pump blood effectively to meet the body's metabolic needs, which causes debilitating symptoms, frequent hospitalizations, and high mortality rates. Historically, the management of heart failure has focused on symptom relief, fluid reduction, and cardiac contractility, often in conjunction with device-based interventions like implanted cardioverter-defibrillators and cardiac resynchronization therapy [1-5]. The unrelenting progression of heart failure, however, continues to be a major clinical concern in spite of recent advancements. Among the complex mechanisms influencing the disease's development are cellular remodeling, cardiac fibrosis, and neurohormonal activation. Researchers and medical professionals have been searching for new therapy strategies that target these basic systems in recent years. One such area of research is the cutting-edge field of gene therapy, where promising gene-editing methods like CRISPR-Cas9 may provide ways to fix genetic abnormalities that cause heart failure. Furthermore, there is great potential for rebuilding damaged heart tissue and regaining function through regenerative medicine techniques including tissue engineering and stem cell therapy [7,8,9,11,14]. Additionally, efforts in precision medicine have gained momentum with the goal of customizing heart failure treatments to each patient's unique profile while accounting for comorbidities, biomarkers, and genetics. Predictive models for early intervention, risk assessment, and individualized therapy recommendations have also been made possible by the integration of AI and machine learning in the management of heart failure. By focusing on the disease's underlying mechanisms, these novel treatments for heart failure have the potential to completely transform the sector, as this narrative review highlights. By investigating these cutting-edge strategies, we seek to offer a thorough understanding of the changing paradigm of heart failure care, encouraging optimism in both patients and physicians [11-20].

Conclusions. From novel pharmacological interventions to innovative device-based therapies, regenerative medicine, and precision care, these advancements offer hope for patients facing this difficult condition. These advancements enable tailored treatment plans, precise risk prediction, and a shift towards more patient-centric care. The combination of data-driven clinical decision-making, multidisciplinary collaboration, and patient empowerment promises improved outcomes and enhanced quality of life for individuals with heart failure. Conclusion: This review has highlighted the multifaceted nature of heart failure management, exploring its complexities, challenges, and promising innovations.

With continued research and dedication, we can look forward to a better future for heart failure patients and a revolutionized care landscape. As we navigate the challenges of cost, accessibility, and ethical considerations, it is evident that the pursuit of emerging therapies and precision medicine in heart failure management is not only a scientific endeavor but also a moral imperative. The future of heart failure care holds the potential to redefine the patient experience, reduce disparities, and, ultimately, save lives.

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