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Heart Failure Management, including Recently Approved Therapeutic Options: An Overview

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Abstract

Heart failure (HF) affects the heart's structure and function. It is considered a complex clinical syndrome attributed to any anatomic or physiologic impairment of the ejection of blood or ventricular filling. The incidence of this clinical condition is increasing and causing a significant impact on healthcare systems worldwide. Since the pathophysiology of HF is well understood, treatment options have had significant advancements. Initially, many compensatory mechanisms are helpful, but over time they contribute to the progression of the disease, such as increased adrenergic activity, renin-angiotensin-aldosterone system activity, and secretion of B-type natriuretic peptide (BNP). These may cause progressive myocardial damage. For this reason, different groups of drugs are used for managing HF, targeting different points of the physiopathology of HF. An instance is the drug combination sacubitril/valsartan, which increases BNP levels while simultaneously inhibiting the renin-angiotensin system (RAS). Other examples include sodium-glucose cotransporter 2 inhibitors (SGLT2i), which lower blood pressure, soluble guanylate cyclase (sGC) stimulators that cause smooth muscle relaxation and vasodilation, beta-blockers (BBs), which lower heart rate and contractility, and mineralocorticoid receptor antagonists (MRAs), which maintain water and electrolyte homeostasis. This article is aimed to identify when these medications are recommended, and to point out the recently FDA-approved SGLT2i and soluble guanylyl cyclase (sGC) stimulator (vericiguat), taking into account their adverse effects, symptoms, and comorbidities of the patient that may worsen the disease process.

Keywords: Heart Failure; Treatment; Sacubitril/Valsartan; Angiotensin Receptor Blocker; Neprilysin Inhibitor; Angiotensin-Converting Enzyme Inhibitors; Sodium-Glucose Cotransporter; Beta Blockers; Mineralocorticoid Receptor Antagonists; Guanylate Cyclase Stimulator

Abbreviations: HF: Heart Failure; FDA: The Food and Drug Administration; BBs: Beta-blockers; MRAs: Mineralocorticoid Receptor Antagonists; SGLT2i: Sodium-glucose Cotransporter 2 Inhibitors; sGC: soluble Guanylyl Cyclase; RAS: Renin-angiotensin System; US: United States; EF: Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; HFrEF: HF with Reduced EF; HFmrEF: HF with mildly reduced EF; HFpEF: HF with preserved EF; NYHA: New York Heart Association; ECG: Electrocardiogram; LV: Left Ventricular; ARBs: Angiotensin Receptor blockers; ARNi: Angiotensin Receptor-neprilysin Inhibitor; BNP: B-type Natriuretic Peptide; Ang II: Angiotensin II; ACEi: Angiotensin-converting enzyme inhibitors; NT-proBNP: N-terminal proBNP; CKD: Chronic Kidney Disease; SGLT: Sodium-glucose Cotransporter; NSAIDs: Non-steroidal Anti-inflammatory Drugs; NO: Nitric Oxide; cGMP: cyclic Guanosine Monophosphate; LDL: Low-density Lipoprotein

Introduction

Globally, heart failure (HF) is one of the significant causes of morbidity and mortality, and it is considered a complex clinical syndrome attributed to any anatomic or physiologic impairment of the ejection of blood or ventricular filling [1,2]. In the United States (US), the statistic shows that more than 5.1 million individuals presented with clinical manifestations of HF and 650,000 new cases per year [1]. Additionally, HF generates an enormous financial burden worldwide with high mortality and hospitalization rates [1,2]. HF is classified according to the left ventricular ejection fraction (LVEF) as HF with reduced EF (HFrEF; with an ejection fraction (EF) <40%), HF with mildly reduced EF (HFmrEF; EF 41%–49%), and HF with preserved EF (HFpEF; EF ≥50%) [1,2]. Furthermore, HF can be classified according to exercise tolerance as New York Heart Association (NYHA) I to IV [2]. The clinical manifestations of HF are nonspecific and may overlap with other medical disorders. Thus, the diagnosis of HF may be burdensome [2]. Although increased B-type natriuretic peptide (BNP) levels can support the diagnosis, normal levels do not rule it out. Consequently, further diagnostic tests are required, including laboratory tests, electrocardiogram (ECG), and echocardiography, including the evaluation of left ventricular (LV) filling pressures (at rest and with exercise stress test) [2]. Numerous pharmacological options can be used to manage HF. The most effective are renin-angiotensin system (RAS) inhibitors, beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and soluble guanylyl cyclase (sGC) stimulators [2]. This review article is aimed to identify when these medications are recommended, mainly the recently FDA-approved SGLT2i and sGC stimulator (vericiguat), taking into account their adverse effects and the symptoms and comorbidities of the patient that may worsen the disease process.

Angiotensin Receptor-neprilysin Inhibitor

Sacubitril/valsartan, a combination of an angiotensin receptor blocker (ARB) and a neprilysin inhibitor, is the first angiotensin receptor-neprilysin inhibitor (ARNi) approved for patients with symptomatic HF [1,2]. In the natriuretic peptide system, the B-type natriuretic peptide (BNP) is involved in diuresis, natriuresis, and smooth muscle cell relaxation [1]. Sacubitril, a neprilysin inhibitor, increases BNP level by inhibiting its breakdown resulting in sodium excretion, vasodilation, and improved cardiac remodeling [1]. However, it also inhibits the breakdown of angiotensin, causing an increase in angiotensin II (Ang II) level, which worsens HF by modulating arterial vasoconstriction, sodium, and water reabsorption, vascular smooth muscle contraction, and aldosterone release [1]. Thus, sacubitril is recommended to be used in combination with a RAS inhibitor. Angiotensin-converting enzyme inhibitors (ACEi) are not recommended in combination with sacubitril because both inhibit the breakdown of bradykinin which induces angioedema [1,2]. For this reason, combining sacubitril with an ARB, such as valsartan is recommended. Valsartan selectively blocks Ang II receptors inhibiting the actions of Ang II, and subsequently improves cardiac dysfunction and remodeling in patients with HF [1,2]. Multiple studies, for instance, the PARADIGM-HF trial and the PIONEER-HF trial, have shown that compared to ACEi, sacubitril/valsartan reduces the risks of cardiovascular mortality and hospitalization by 20% and 21%, respectively. Additionally, it reduces all-cause mortality, rehospitalization, and the levels of N-terminal proBNP (NT-proBNP) without increasing the rates of adverse reaction [1,2]. ARNi effectively reverses LV remodeling along with right ventricular and atrial remodeling in HFrEF patients and subsequently reduces HF progression [1]. Moreover, ARNi enhances cardiac function and exercise capacity improving quality of life. Since ACEi/ARBs often cause worsening renal failure, especially in chronic kidney disease (CKD) patients, sacubitril/valsartan could be a therapeutic option in patients with HF and renal impairment [1]. Few studies have reported that sacubitril/valsartan might have beneficial antiarrhythmic and metabolic effects, for example, reducing ventricular arrhythmias and improving blood glucose and uric acid levels [1]. However, the exact mechanisms are unknown, and further studies are required. As a result, ARNi has been given a class 1A recommendation in the recently released HF management guideline to lower mortality and morbidity in patients with HFrEF and NYHA classes II to III [2]. Furthermore, sacubitril/valsartan is recommended (class 1B-R) to replace ACEi or ARB in patients with chronic symptomatic HFrEF who tolerate an ACEi or ARB [2]. However, patients with a history of angioedema should not receive ARNi, as well as those using ACEi or whose last dose of ACEi was within 36 hours [2]. Some common adverse reactions are symptomatic hypotension, angioedema, headache, dizziness, cough, hyperkalemia, and renal dysfunction [1,2]. Nevertheless, hyperkalemia and renal dysfunction were less frequent with ARNi than with ACEi [1]. Compared with ACEi/ARBs, sacubitril/valsartan is considered safe and well-tolerated in patients with HFrEF [1,2].

Sodium-glucose Cotransporter 2 Inhibitors

The active process of glucose reabsorption from the glomerular filtrate is linked to sodium and requires a carrier protein known as a sodium-glucose cotransporter (SGLT). One of the isomers found exclusively in the epithelial cells of the proximal renal tubule is SGLT2, where more than 90% of glucose and 65% of sodium reabsorption occur [3,4]. Therefore, gliflozins, an SGLT2i, can lower renal tubular reabsorption of glucose and sodium. Consequently, this causes better glycemic control and lowers blood pressure due to increased excretion of water in the urine [3,4]. According to multiple clinical trials, a significant advantage of gliflozin is that it requires only one dose per day, whether taken with or without food, with a standard dose of 10 mg daily for dapagliflozin or empagliflozin [4]. The Dapagliflozin and Prevention of Adverse Outcomes in Heart

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Failure (DAPA-HF) trial showed that dapagliflozin can cause a significant reduction in cardiac mortality or hospitalization for HF (the primary endpoint) (hazard ratio, 0.74; 95% CI, 0.65 to 0.85), along with a significant reduction in hospitalization for HF (31%) [3]. However, two limitations were found in this study: (a) only a small portion of participants enrolled had HF with an EF below 40%, and (b) 55% of those enrolled patients did not have type 2 diabetes [3]. In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial, the same design of the DAPA-HF trial was used. Nevertheless, unlike the DAPA-HF trial, patients with more severe systolic dysfunction were included in this study. Furthermore, cardiovascular benefit was observed in both type 2 diabetes and non-diabetic patients. Further benefits were noted with improvement of the NT-proBNP levels, renal function, and baseline glucose levels [3]. Data from two studies have demonstrated that SGLT2i is effective in the treatment of HF. In addition, significant reductions in cardiovascular mortality and hospitalization rates were reported. As a result of the previous trials, gliflozins that have been approved are Dapagliflozin and Empagliflozin according to the DAPA-HF and EMPEROR-Reduced trials, respectively [3]. SGLT2i can result in mild dehydration due to the increased osmolarity of the urine [3,4]. For this reason, they should be used cautiously in patients with comorbidities that might induce acute renal injury (hypovolemia, HF, liver injury), as well as in combination with other drugs that can cause acute renal injury (Non-steroidal anti-inflammatory drugs (NSAIDs), ACEi/ARBs, diuretics) [4]. The most common side effects of SGLT2i are mycotic genital infections associated with the glycosuric action of these agents [3]. These infections have been reported to be more frequent in women than in men [3]. Although uncommon, diabetic ketoacidosis can happen, especially in older patients with volume depletion, highlighting the significance of knowing the volume status of patients receiving this class of medication [4].

Soluble Guanylate Cyclase Stimulator

There is increased inflammation and vascular dysfunction in HF resulting in lower nitric oxide (NO) bioavailability, which leads to a reduction in cGMP synthesis. This reduction causes systemic, coronary, and renal microcirculatory dysfunction, which may cause progressive myocardial damage and additional inflammation [5]. For this reason, the FDA recently approved a novel oral soluble guanylate cyclase (sGC) stimulator for HF. Vericiguat, also known as Verquvo, is a new drug that directly stimulates soluble guanylate cyclase (sGC) by itself and, synergistically with NO, produces more cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and vasodilation, which result in improving cardiac function. The efficacy and benefits of vericiguat were evaluated in some experimental studies that suggested multiple potential benefits of sGC stimulators, including prevention, or even reversal, of LV hypertrophy and fibrosis as well as reduction of LV afterload due to systemic and pulmonary vasodilation [5]. For instance, the SOCRATES-REDUCED study enrolled 456 patients with LVEF of less than 45% and a recent episode of HF decompensation, defined by worsening HF symptoms requiring hospitalization or outpatient administration of intravenous diuretics, signs of congestion, and elevated BNP level, compared vericiguat versus placebo. Comparison between vericiguat 10 mg and placebo achieved statistical significance (p=0.048). Vericiguat therapy did not affect the hemodynamic function and appeared safe, with lower rates of serious adverse events than placebo [5]. Another important study is Victoria, a randomized, double-blind, and placebo-controlled trial that assigned 5050 patients with chronic HF (NYHA class II, III, or IV) and an EF of less than 45% to receive vericiguat (10 mg one dayli) or placebo, in addition to standard medical therapy [6]. The principal outcome was death from cardiovascular causes or first-time hospitalization for HF, and it was found that vericiguat was superior to placebo. The difference favoring vericiguat appeared after approximately three months of treatment and persisted throughout the trial. The 10% relative difference between the groups in the primary composite outcome in this high-risk population at a median follow-up of 10.8 months translated into an absolute event-rate reduction of 4.2 events per 100 patients per year [6]. Although vericiguat is not considered the first choice for HF, it has specific indications such as in patients with NYHA II-IV, patients who need outpatient IV diuretics, and adults with symptomatic chronic HF with an EF less than 45%. Another indication for its use is to decrease the risk of cardiovascular death and HF hospitalization following a hospitalization due to HF [6]. Because vericiguat was recently approved, there are no known long-term side effects. Some literature mentions low blood pressure and anemia as the most common side effects, but it is still unclear. Since vericiguat causes vasodilation, precautions must be taken when combined with medication with a similar effect. Something important to highlight is that no data was found on the use of vericiguat in pregnant patients or breastfeeding. Therefore, pregnancy will be a contraindication until enough data can support its use.

Beta-Blockers

The sympathetic nervous system activation produced by HFrEF brings detrimental consequences such as increased myocardial energy demands, elevated heart rate, and adverse remodeling [7]. The use of BBs, which are widely studied, prevents the cascade of effects produced by the surge of catecholamines. The contractility of the myocardium depends on inotropic and chronotropic effects. The beta-blockade restores this due to the upregulation of the beta-1-receptor [7,8]. Additionally, heart rate reduction, which produces a decrease in myocardial oxygen demands and an increase in myocardial perfusion, is an important therapeutic goal offered by the beta blockade [9]. Maladaptive changes in dimension, mass, and shape of the heart due to increased volumes and neurohormonal activation are defined as remodeling of the heart. BBs decrease end-systolic

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and end-diastolic volumes, resulting in improved LV remodeling and systolic function six months after initiation [7,10]. Blocking the effects of RAS system activation is substantial in preventing HF progression. For this reason, combining drugs such as ACEi, ARBs and BBs are the cornerstone of HF therapy [9]. The prompt initiation of BBs such as carvedilol, metoprolol succinate, and bisoprolol in symptomatic or asymptomatic HF patients is related to a decrease in disease progression, mortality, and improvement of clinical symptoms. However, long-term treatment should be maintained even if symptoms do not improve to reduce the risk of major cardiovascular events [10,11]. SOLVD prevention trial (which included 80% with previous myocardial infarction) and the SAVE (Survival and Ventricular Enlargement) trial studied the use of beta blockers among patients with asymptomatic LV systolic dysfunction. They found that the administration of beta blockers and ACEi reduced mortality and hospitalization rate [7,10]. It is essential to notify the patient about the importance of continued use of BBs because several trials have shown that symptoms can be worse in the first two weeks of treatment before any improvement is observed. Moreover, initiate with very low doses, and try to double at intervals of two weeks until the target dose is achieved. Most of the benefits of this therapy are dose-dependent [9]. Absolute contraindications for using BBs in HF patients are second or third-degree atrioventricular block in the absence of a pacemaker. Bradycardia with a rate lower than 50 beats per minute is another contraindication [10]. Nonselective and selective beta blockers share many side effects such as depression, anxiety, weight gain, bradycardia, asthma exacerbation, and alteration in the metabolism of triglycerides and low-density lipoprotein (LDL). Nevertheless, when balancing the benefits and side effects of BBs, the benefits outweighed the desireless effects [11].

Mineralocorticoid Receptor Antagonists

Aldosterone, a mineralocorticoid steroid hormone, works mainly in the distal convoluted tubule, generating water and sodium reabsorption and potassium excretion, which is essential to maintain water and electrolyte homeostasis. However, it is also involved in the pathophysiology of HF due to its enhancing effect on cardiac remodeling and contributing to overtime worsening of EF. Thus, spironolactone, a mineralocorticoid receptor antagonist, hinders this cardiac effect and is indicated in HF [12]. According to AHA 2022, the use of MRAs, spironolactone or eplerenone, is recommended in patients with HFrEF and NYHA with class II to IV symptoms to reduce morbidity and mortality [2]. The Randomized Aldactone Evaluation Study (RALES) showed the efficacy of aldosterone. This study enrolled a total of 1663 participants with severe HF. The participants were randomly selected to receive conventional therapy plus placebo or conventional therapy plus spironolactone. This trial showed a significant reduction in all causes of death in the spironolactone group compared to placebo [2]. Spironolactone and eplerenone reduce the excretion of potassium, therefore increasing the risk of hyperkalemia [13]. The most common and essential adverse effect to be considered is hyperkalemia. In addition, dehydration, hyponatremia, nausea, vomiting, and diarrhea are also common. Some important adverse effects to be considered with spironolactone due to its antiandrogenic effect are gynecomastia in men, loss of libido, and feminization [14]. Some contraindications of MRAs therapy include renal function below 30ml/min/1.73m2 and serum potassium values over 5mEq/L. Therefore, patients at risk of renal dysfunction or hyperkalemia require close monitoring [2,13].

Conclusion

Advances in medicine have led to new medical discoveries and to create new treatment options for conditions that are challenging to manage. HF is a complex condition that historically has played a substantial role in morbidity and mortality. Therefore, numerous studies emphasize the significance of new treatment options with the best results and fewest adverse effects. This article is aimed to overview the new and recently approved therapeutic regimens for HF and compare them with the standard regimen. The effectiveness of these new drugs were demonstrated in many clinical trials. After a detailed review of numerous treatment options for each HF stage according to the NYHA/AHA 2022 guidelines, we concluded the following: (a) In terms of newer and combined therapies, ARNi has shown to be effective reversing LV remodeling and subsequently reducing HF progression, (b) SGLT2i is effective for treating HF with or without diabetes, (c) both ARNi and SGLT2i have demonstrated to significantly decrease cardiovascular mortality and hospitalization rates due to HF, (d) Vericiguat has shown promising results in terms of both slowing the progression of the disease and reversing cardiac dysfunction in severe or refractory HF stages, (e) BBs can be reserved for patients with HF who are in the initial stages of the disease and to prevent worsening of the condition, and (f) MRAs should only be utilized in advanced stages of HF (well-known comorbidity) and is not recommended in patients with impaired renal function. Patients can have different stages of HF, as mentioned previously in this review. Therefore, we must think of HF as a complex condition, and acknowledge the importance of an accurate multidisciplinary assessment of HF patients, whether they have comorbidities or not.

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