Individualizing the treatment of patients with heart failure with reduced ejection fraction: a journey from hospitalization to long-term outpatient care

Carlos Escobar[a], Juan Luis-Bonilla[b], Maria G. Crespo-Leiro[c], Alberto Esteban-Fernández[d], Nuria Farré[e], Ana Garcia[f] and Julio Núñez[g]

[a]Cardiology Service, Hospital Universitario La Paz, Madrid, Spain; [b]Cardiology Service, Hospital San Juan De La Cruz, Jaen, Spain; [c]Cardiology Service, Complexo Hospitalario Universitario A Coruña (CHUAC)-CIBERCV, A Coruña, Spain; [d]Cardiology Service, Hospital Universitario Severo Ochoa, Madrid, Spain; [e]Cardiology Service, Hospital Del Mar, Barcelona, Spain; [f]Cardiology Service, Hospital Clinic I Provincial De Barcelona, Barcelona, Spain; [g]Cardiology Service, Hospital Clinico de Valencia, Valencia, Spain.

CONTACT Carlos Escobar, escobar_cervantes_carlos@hotmail.com Cardiology Service, Hospital Universitario La Paz, Madrid, Spain

ABSTRACT

*Introduction***.** Despite the relevant advances achieved thanks to the traditional step-by-step therapeutic approach, heart failure with reduced ejection fraction (HFrEF) remains associated with considerable morbidity and mortality. The pathogenesis of HFrEF is complex, with the implication of various neurohormonal systems, including activation of deleterious pathways (i.e. renin-angiotensin-aldosterone, sympathetic, and sodium-glucose cotransporter-2 [SGLT2] systems) and the inhibition of protective pathways (i.e. natriuretic peptides and the guanylate cyclase system). Therefore, the burden of HF can only be reduced through a comprehensive approach that involves all evidence-based use of available HF drugs targeting the neurohormonal systems involved.

Areas covered. We performed a critical analysis of evidence from recent clinical trials and assessed the effects of HF therapies on hemodynamics and renal function.

Expert opinión. HF therapy must be adapted to the clinical profile (i.e. congestion, blood pressure, heart rate, renal function, and electrolytes). Consequently, blood pressure is reduced by beta blockers, renin-angiotensin-aldosterone system inhibitors, sacubitril/valsartan, and, minimally, by SGLT2 inhibitors and vericiguat; heart rate decreases with beta blockers and ivabradine; and renal function is impaired and potassium are levels increased with renin-angiotensin-aldosterone

system inhibitors and sacubitril/valsartan. Practical recommendations on how to individualize HF therapy according to patient profile are provided.

KEYWORDS:
Beta blockers; heart failure; ivabradine; sacubitril/valsartan; renin angiotensin aldosterone system inhibitors; SGLT2 inhibitors; vericiguat

1. Introduction

Heart failure (HF) is a chronic condition in which the heart muscle is unable to pump enough blood to meet the body's requirements for oxygen and blood that reaches epidemic numbers [1,2]. In Europe, it has been estimated that the incidence of HF is about 3.20 cases per 1000 person-years and the prevalence reaches 2% [1,3,4]. In the United States, around 6 million adults ≥20 years have HF [5]. Moreover, due to aging of the population, as well as the higher prevalence of predisposing factors, such as hypertension and diabetes, the burden of HF is expected to increase in the coming years [2,3,5]. In fact, it is projected that the prevalence of HF will increase by 46% in 2030 [5].

HF is associated with considerable morbidity and mortality [5]. Thus, data from Medicare showed a slight decline in the overall 1-year mortality of HF between 1998 and 2008, but it still reached nearly 30% [6]. In addition, data from 2000 to 2010 showed a 5-year mortality rate close to 50% [7]. The reduction in mortality observed in recent decades has been attributed mainly to the evidence-based use of HF therapies, including renin-angiotensin-aldosterone system (RAAS) inhibitors (i.e. angiotensin-converting enzyme inhibitors [ACEi], angiotensin-receptor blockers [ARB], mineralocorticoid receptor antagonists [MRA]), beta blockers, coronary revascularization, and devices [8]. Nevertheless, mortality rates remain high, with no clear improvements over the last 10 years [2], probably because of the infrequent use of HF drugs in clinical practice [4,9–11], but also because of the need for new treatment alternatives [12–14].

With regard to morbidity, HF-related hospitalization rates have been increasing over time [15]. Of note, a significant and constant increase in hospitalizations for HF has been reported in recent years [16,17]. Of note, rates of rehospitalization and cardiovascular death increase dramatically in patients previously hospitalized for HF [18–20]. A study from 2021 reported that up to 30% of patients were admitted for HF after 1 year of follow-up and that mortality rates reached 8% during admission [4]. Elsewhere, in-hospital mortality among patients hospitalized with HF, was around 9% – although this reached nearly 15% within the first year of follow-up – and the annual readmissions rate was 33% [21]. As a result, to reduce the burden of HF, it is mandatory to prescribe evidence-based HF therapies [12–14]. Unfortunately, adherence to HF medication after hospitalization decreases over time [22], leading to high rehospitalization rates [23]. Finally, total costs for HF are considerable, mainly due to hospitalization. Only a small proportion are due to medication. Therefore, the use of drugs that reduce hospitalization for HF will translate into a significant reduction in healthcare costs [24–27].

In summary, HF with reduced ejection fraction (HFrEF), defined as symptoms and signs of HF and left ventricular ejection fraction (LVEF) ≤40%, is associated with high morbidity and mortality, and this can only be reduced through a comprehensive approach with the evidence-based use of all currently available HF drugs. In this manuscript, recommendations we focused on patients with HFrEF.

2. Pathogenesis of HFrEF: a change of paradigm is warranted

Activation of the RAAS and sympathetic nervous system has been traditionally involved in the pathogenesis of HFrEF [28– 31]. In this context, the main target of HFrEF treatment was largely limited to inhibition of these systems (using RAAS inhibitors and beta blockers) [32]. However, the pathogenesis of HFrEF is more complex and challenging, with the implication of several neurohormonal systems, including activation of deleterious pathways, such as RAAS, the sympathetic nervous system, and the sodium-glucose cotransporter-2 (SGLT2) system, and the inhibition of protective pathways, such as the natriuretic peptide pathway and the guanylate cyclase system (Figure 1) [33–41]. Although these neurohormonal systems are designed to maintain cardiovascular homeostasis in the short term, chronic activation/inhibition of the pathways induces deleterious changes in the heart, kidneys, and vasculature, and this translates into

impairment of HF [30]. For example, HFrEF is associated with nitric oxide deficiency, decreased soluble guanylate cyclase activity, and cGMP production, which can damage the cardiovascular and renal systems. Stimulation of soluble guanylate cyclase with vericiguat will improve/reverse these alterations [35–38]. Therefore, the etiopathogenesis of HFrEF is complex, as many neurohormonal systems are implicated. As a result, HF burden can be reduced only through a comprehensive approach that targets all these systems [42,43].

3. Traditional approach to patients with HFrEF

The 2016 ESC guidelines for patients with symptomatic HFrEF recommend the use of ACEi (or ARB if ACEi are not tolerated/ contraindicated) and beta blockers, at the maximum tolerated doses. If the patient remains symptomatic, an MRA should be added. If this proves insufficient, ACEi or ARB can be switched to sacubitril/valsartan or ivabradine added in patients with a normal sinus rhythm and heart rate >70 bpm [32].
These recommendations were based on clinical trials that had shown the benefits of using these drugs in this population. Thus, in patients with chronic HF and LVEF ≤35% (90% New York Heart Association [NYHA] functional class II–III), the SOLVD study showed that the addition of enalapril to standard treatment significantly reduced the risk of all-cause mortality by 16% and combined all-cause mortality and HF-related hospitalization by 26% [44]. In patients with severe chronic HFrEF, carvedilol reduced all-cause mortality by 35% and combined all-cause mortality and any hospitalization rate by 24% [45]. In the CIBIS II trial, in patients with LVEF ≤35% and NYHA III–IV, bisoprolol decreased all-cause mortality by 34% and combined cardiovascular mortality or cardiovascular hospitalization by 21% [46]. The RALES trial demonstrated that among HF patients with LVEF ≤35%, NYHA III–IV, and HF for >6 weeks, spironolactone reduced all-cause mortality by 30% and cardiac hospitalization by 35% [47]. In the EMPHASIS-HF trial, eplerenone reduced the risk of combined cardiovascular mortality or HF-related hospitalization by 37%. In the case of all-cause and cardiovascular mortality in NYHA II, LVEF <30% or LVEF 30– 35% and QRS >130 ms, recent cardiovascular hospitalization, or elevated natriuretic peptides, the risk was reduced by 24% [48]. In symptomatic patients with LVEF ≤40% and intolerance to ACEi, candesartan reduced combined cardiovascular mortality and HF-related hospitalization

by 23% [49]. In the SHIFT study (patients with LVEF ≤35%, NYHA II–IV, prior HF-related hospitalization, sinus rhythm, and heart rate ≥70 bpm), ivabradine reduced the risk of combined cardiovascular mortality and HF-related hospitalization by 18%, HF-related hospitalization by 26% and HF-related mortality by 26% [50].

Unfortunately, despite the benefits shown in these clinical trials, morbidity and mortality remain very high. For example, the results of the SHIFT trial (data from 2010) showed that in the ivabradine arm, after a median follow-up of 22.9 months, 16% of patients were hospitalized for worsening HF, 14% of patients died of a cardiovascular condition, and 24% were hospitalized for worsening of HF or died of cardiovascular causes [50].

These data show that the step-by-step approach proposed by the 2016 ESC guidelines was insufficient, as HFrEF is a progressive condition. Therefore, new HF treatment strategies are necessary to provide a more holistic approach [42,43].

4. New evidences for patients with HFrEF

In recent years, results from several clinical trials show the benefits of new HF drugs. The PARADIGM-HF trial included patients with symptomatic HF and LVEF ≤40% treated with sacubitril/valsartan or enalapril, in addition to standard HF therapy. After a median follow-up of 27 months (the study was stopped prematurely), sacubitril/valsartan significantly reduced the risk of cardiovascular mortality or first HF- related hospitalization by 20%, all-cause mortality by 16%, cardiovascular mortality by 20%, and HF-related hospitalization by 21% [51]. The DAPA-HF trial included patients with symptomatic HF and LVEF ≤40% with and without diabetes, revealing a reduction of 26% in the risk of combined cardiovascular mortality or worsening of HF, 18% in the risk of cardiovascular mortality, 17% in the risk of all-cause mortality, and 30% in the risk of worsening HF with dapagliflozin compared with placebo [52]. Similarly, the EMPEROR-Reduced trial included patients with symptomatic HF and LVEF ≤40% with and without diabetes and showed a reduction of 25% in the risk of combined cardiovascular mortality or worsening HF and 30% in the number of HF-related hospitalizations with empagliflozin compared to placebo [53]. In recently hospitalized symptomatic HF patients with EF <45%, the VICTORIA trial showed a 10% reduction in the risk of combined cardiovascular mortality or HF-related hospitalization with vericiguat, compared with placebo [54]. The baseline clinical characteristics and

outcomes of these trials (PARADIGM HF, DAPA-HF, EMPEROR-Reduced, and VICTORIA) are summarized in Table 1. Although the trials are not comparable, as the inclusion/exclusion criteria and baseline clinical characteristics were different, all of them revealed significant improvements in cardiovascular mortality and HF-related hospitalizations compared with standard treatment (number needed to treat [NNT] between 19–37). In fact, a recent study showed that compared with the traditional approach (ACEi or ARB and beta blockers), the one-step (comprehensive) therapy consisting of sacubitril/ valsartan, MRA, beta blockers, and SGLT2 inhibitors led to significant reductions in cardiovascular death or admission to hospital with HF (62%), cardiovascular death (50%), HF hospitalization (68%), and all-cause mortality (47%), strongly suggesting the need to target all neurohormonal systems in a first comprehensive approach (Figure 2) [55].

5. Potential relevance of stimulating soluble guanylate cyclase in the management of patients with HFrEF

HFrEF patients are characterized by marked impairment of the nitric oxide–soluble guanylate cyclase-cGMP system, leading to major alterations in various organs and vascular beds. In the heart, progressive myocardial stiffening, hypertrophy, ventricular remodeling, inflammation, and fibrosis have been reported. Increased sodium and fluid retention, fibrosis, and decreased blood flow have been described in the kidney. In addition, inflammation and arterial constriction are increased in the vasculature, as is vascular stiffness, thus promoting endothelial dysfunction [35–38,56]. Vericiguat is an oral direct soluble guanylate cyclase stimulator that could potentially improve/reverse these alterations, leading to an improvement in HF outcomes, as observed in clinical trials [56].

In SOCRATES-REDUCED, although no significant differences were observed overall for the change in NT-proBNP level at 12 weeks among patients with HFrEF, there was a dose- response relationship between vericiguat and NT-proBNP, such that the higher dose, the greater the reduction [57]. VICTORIA was a phase 3, randomized clinical trial in which 5,050 symptomatic patients (chronic HF, EF <45%, elevated natriuretic peptides and evidence of worsening HF [HF hospitalization within 6 months or need for intravenous diuretic therapy within the previous 3 months before randomization])

received vericiguat (target dose 10 mg once daily) or placebo, in addition to standard therapy. After a median follow-up of 10.8 months, vericiguat reduced the risk of cardiovascular death or first HF hospitalization by 10% (hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.82–0.98; P = 0.02, NNT = 24), driven mainly by a reduction in HF-related hospitalization (NNT = 31). Vericiguat also significantly reduced the risk of death from any cause and HF hospitalization (HR 0.90; 95% CI 0.83–0.98; P = 0.02) (Table 1) [54]. The benefits of vericiguat were independent of the use of concomitant HF treatment, including sacubitril/valsartan, and time since HF- related hospitalization or an HF-related decompensation episode [54,58]. This suggests that vericiguat can be used regardless of baseline HF treatment, during hospitalization, at early discharge, or during follow-up and that its use should not be delayed until optimization of the remaining HF treatment [54,58]. Of note, patients with an estimated glomerular filtration rate ≥15 mL/min/1.73 m^2 were included in the VICTORIA trial, and the benefits of vericiguat were independent of renal function. Since vericiguat has no impact on renal function or electrolyte levels, it could prove particularly useful in patients with chronic kidney disease [59]. However, as a subanalysis showed that the benefit of vericiguat seems limited to patients with NT-proBNP ≤8000 pg/mL (particularly <4000 pg/mL), some patients with higher levels of natriuretic peptides would likely require intensification of diuretic treatment before starting treatment with vericiguat [60].

Regarding side effects in the VICTORIA trial, vericiguat was well tolerated, with no significant increase in the risk of symptomatic hypotension or syncope [54]. In summary, vericiguat is a new treatment with an added value in the management of patients with HFrEF, particularly those with previous decompensated HF, exhibiting further benefits beyond the standard approach to HF.

6. What do international guidelines recommend?

Albeit with some variations, all 2021 and 2022 international HF guidelines have moved from a step-by-step approach to a comprehensive approach [12–14]. Thus, the 2021 ESC guidelines recommend the use of ACEi or sacubitril/valsartan (preferred), beta blockers, MRA, and SGLT2 inhibitors as baseline therapy among patients wIth HFrEF to reduce the risk of HF-related hospitalization and death. If the patient has history of worsening HF, vericiguat should be considered to reduce the risk of hospitalization and

cardiovascular death. Although the recommendation was IIb for vericiguat, as the power of the effect was <20%, this could have been higher (IIa), given the robustness of the results of the VICTORIA trial [61]. Lastly, if the patient remains symptomatic, in sinus rhythm, with a heart rate >70 bpm, ivabradine should be considered to reduce the risk of HF-related hospitalization and cardiovascular death (Figure 3, Table 2) [12].

The 2022 AHA/ACC/HFSA guideline recommends sacubitril/ valsartan (over ACEi or ARB), beta blockers, MRA and SGLT2 inhibitors as baseline therapy; if the patient remains symptomatic, other therapies, such as hydralazine and isosorbide dinitrate, ivabradine or vericiguat can be considered, depending on the patients' clinical characteristics (Figure 3) [13]. As first-line therapy, the 2021 Canadian guidelines recommend sacubitril/valsartan (over ACEi or ARB), beta blockers, MRA, and SGLT2 inhibitors. In the case of persistence of symptoms the addition of ivabradine or vericiguat should be considered, if suitable (Figure 3) [14].

In summary, all guidelines agree that optimization of HFrEF therapy cannot be delayed, as HF is a progressive condition [62,63]. While it is important to achieve the maximum tolerated dose of each drug, targeting the different neurohormonal systems that underline the pathogenesis of HF should be considered a priority, and treatment should not be postponed [42,43].

7. Implementation of guided HF therapy in clinical practice

Although the goal of treatment in all cases is to use all therapeutic groups targeting the different neurohormonal systems, not all drugs can be prescribed, because of intolerance, side effects, or contraindications. In this context, it is important to know the effects of the various drugs on different variables of interest, particularly hemodynamics and renal function. Table 3 and Figure 4 summarize the impact of guided HF therapy on blood pressure, heart rate, potassium levels, and renal function, as well as the recommendations about how to manage side effects [12–14].

ACEi and ARB, as well as angiotensin receptor-neprilysin inhibitors (ARNI, albeit to a lesser extent), can reduce blood pressure, diminish renal function, and increase potassium levels. They can be started in outpatients and in hospitalized HF patients, particularly in those who are hemodynamically stable. Before initiation, it is important to check renal function and electrolyte levels. Uptitration should be at intervals of no less than 2 weeks,

with regular monitoring of blood pressure, renal function, and electrolyte levels. In the case of switching from ACEi to sacubitril/valsartan, a washout period of at least 36 hours is required (not necessary in the case of switching from ARB) [12–14,64,65].

Beta blockers can reduce blood pressure and heart rate and cause asthenia. They can be started in outpatients and in hospitalized HF patients, although stabilization and relief of congestion are desirable. Caution should be observed in patients with recent decompensation. Uptitration should be performed at intervals of no less than 2 weeks (in some patients this interval may be longer), with regular monitoring of blood pressure, heart rate, and clinical status (i.e. congestion, fatigue) [12–14,64,65].

MRA can decrease renal function and increase potassium levels, although they have little impact on blood pressure. They can be started in outpatients or in the hospital. Before starting, it is important to check renal function and electrolytes. Uptitration should be considered after 4–8 weeks, with regular monitoring of renal function and electrolyte levels [12– 14,64,65].

SGLT2 inhibitors may have little impact on blood pressure and renal function, particularly in patients with hypovolemia or taking high-dose diuretics. As a result, when starting SGLT2 inhibitors (in the community or in hospital), it is important to monitor fluid balance and blood pressure and adjust the dose of diuretics, if necessary. No dose adjustment is required. Although the risk of hypoglycemia is low, it must be considered, mainly in the case of concomitant treatment with insulin and/or sulfonylurea (the dose of concomitant therapy should be reduced if required) [12–14,64,65].

Ivabradine decreases heart rate and can cause phosphenes. It is recommended in stable outpatients. Considering that most patients are also taking beta blockers, heart rate and clinical status should be monitored during uptitration at intervals of no less than 2 weeks. In the case of persistent/permanent atrial fibrillation, ivabradine should be stopped until sinus rhythm is restored [12–14,64,65].

Finally, vericiguat may have a minimum effect on blood pressure. However, if symptomatic hypotension or systolic blood pressure <90 mmHg is recorded, we should consider reducing the dose or discontinuing therapy. Vericiguat has not been studied in patients with systolic blood pressure <100 mmHg or symptomatic hypotension before starting treatment. Vericiguat can be started in outpatients, during HF- related

hospitalization, or at discharge, as required. Uptitration should be at intervals of no less than 2 weeks, with regular monitoring of blood pressure and clinical status [66].

Therefore, in order to implement guided HF therapy in clinical practice, it is important to individualize treatment based on the patient's clinical profile, with the aim of targeting the main neurohormonal systems involved in the pathogenesis of HFrEF. Table 4 and Figure 5 present a series of practical recommendations on the use of different HFrEF drugs according to blood pressure, heart rate, renal function, potassium levels, and history of atrial fibrillation. These parameters should be taken into account not only in the initial approach, which can be in the outpatient setting or during hospitalization for HF, but also during follow-up. While dosing and uptitration should also be individualized according to these parameters, priority should be given to targeting neurohormonal systems [12–14,64–66]. On the other hand, the use of loop diuretics should be limited to relief of congestive symptoms in order to achieve a euvolemic state [12]. Remarkably, the addition of oral potassium-binding agents could facilitate the use of RAAS inhibitors in patients with hyperkalemia [67]. Other factors that should also be taken into account as part of comprehensive management in patients with HF include drug-drug interactions, contraindications, and side effects [68].

8.Conclusions

Despite traditional HF treatments, morbidity and mortality remain unacceptably high. The pathogenesis of HFrEF is complex, with the implication of various neurohormonal systems, leading to activation of deleterious pathways and inhibition of protective pathways. As a result, to provide further benefits, it is necessary to implement guided HF therapy with the aim of targeting the neurohormonal systems implicated in the pathogenesis of HF. However, as HF therapy must be adapted to the patient's clinical profile according to factors such as blood pressure, heart rate, renal function, electrolyte levels, and congestion, practical recommendations are warranted.

9.Expert opinion

While evidence from clinical trials is necessary to determine the efficacy and safety of a drug and to obtain regulatory approval, the fact is that these studies are performed under ideal conditions (i.e. strict inclusion and exclusion criteria, close follow-up), and the evidence gained cannot always be applied to the whole population in clinical practice [69]. Treating patients with HFrEF is challenging owing to the fragile balance between hemodynamics, renal function, congestive symptoms, activation of deleterious neurohormonal systems, and inhibition of protective pathways [40,41]. In addition, patients with HFrEF have many comorbidities and may be subject to drug-drug interactions with concomitant treatments [4,11]. Furthermore, HF therapies may have a direct impact on these parameters. For example, blood pressure is reduced by beta blockers, RAAS inhibitors, sacubitril/valsartan and, to a lesser extent, SGLT2 inhibitors and vericiguat. Heart rate decreases with beta blockers and ivabradine, and RAAS inhibitors and sacubitril/valsartan, may have a negative impact on renal function and potassium levels [12–14,64–66]. In addition, some conditions or comorbidities may contraindicate or limit the use of some drugs (e.g. beta blockers in patients with asthma, ivabradine in patients with atrial fibrillation) [12–14].

Despite the available evidence and the recommendations of clinical practice guidelines, many real-world patients are not taking guided HF therapies. Thus, the PATHWAYS study (nearly 20,000 adults seeking care for HF between 2017 and 2019 in Spain) showed that around 80% of patients were taking ACEi, ARB, and ARNI, two thirds beta blockers, 28% MRA, and less than 3% ivabradine and SGLT2 inhibitors [11]. These percentages must be improved if the burden of HF is to be reduced.

Previous educational programs based on only evidences from clinical trials and guidelines have failed. So, in this manuscript, the use of simple and practical algorithms according to clinical profile of patients are proposed in order to overcome therapeutic inertia in clinical practice. Although other authors have proposed a similar approach [66], our algorithm is easier to apply, as fewer variables have been considered for each recommendation. Furthermore, in contrast to other proposals that are limited to a first recommendation [66], we extend the recommendations throughout follow-up. This is relevant, as not only is it important to prescribe guided HF therapies targeting all neurohormonal systems, but we must also try to achieve the highest recommended doses

with a good tolerability profile. Thus, the CHAMP-HF Registry of outpatients in the United States with chronic HFrEF receiving at least 1 oral medication for the management of HF showed that among patients taking ACEi/ARB, ARNI, and beta blockers, only 17%, 14%, and 28%, respectively, received the recommended target doses [70]. In this context, our approach could also facilitate uptitration of guided HF therapies.

In any case, the next step is to implement these recommendations in clinical practice and perform specific studies to analyze whether they facilitate a more appropriate use of guided HF therapies and lead to a reduction in the burden of HFrEF in the coming years.

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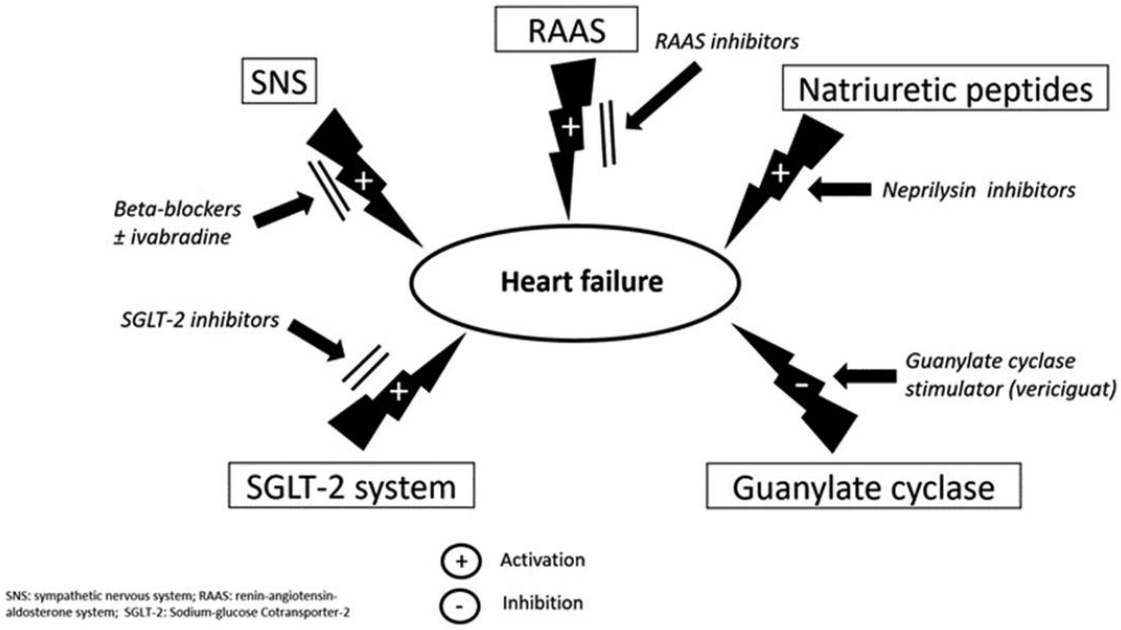

Figure 1. Neurohormonal systems involved in the pathogenesis of heart failure.

Table 1. Baseline clinical characteristics and outcomes of patients included in the PARADIGM HF, DAPA-HF, EMPEROR-Reduced, and Victoria studies.

	PARADIGM HF (N = 8,399) Sacubitril/valsartan	DAPA-HF (N = 4,744) Dapagliflozin	EMPEROR-Reduced (N = 3,730) Empagliflozin	VICTORIA (N = 5,050) Vericiguat
Baseline clinical characteristics				
Age, years	64	66	67	68
Sex, male, %	79	76	76	76
NYHA functional class III–IV, %	25	32	25	41
LVEF, %	30	31	28	29
NT-proBNP (median), pg/mL	1,608	1,437	1,906	2,816
HF hospitalization, %				
<3 months	19	8	NR	67
<6 months	31	16	NA	84
eGFR, mL/min/1.73 m^2	68	66	62	62
Outcomes				
Primary endpoint	First HF hospitalization or CV death	HF worsening or CV death	First HF hospitalization or CV death	First HF hospitalization or CV death
Follow-up, months (median)	27	18	16	11
Primary endpoint event rate (control arm), events per 100 patient-years	13.2	15.6	21.0	37.8
Primary endpoint				
HR (95% CI)	0.80 (0.73–0.87)	0.74 (0.65–0.85)	0.75 (0.65–0.86)	0.90 (0.82–0.98)
ARR, %	2.7	4.0	5.2	4.2

NNT	37	25	19	24
CV death				
HR (95% CI)	0.80 (0.71–0.89)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.93 (0.81–1.06)
ARR, %	1.5	1.4	0.6	1.0
NNT	67	71	167	100
First HF-related hospitalization				
HR (95% CI)	0.79 (0.71–0.89)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.90 (0.81–1.00)
ARR, %	1.6	2.9	4.8	3.2
NNT	63	35	21	31

ARR: absolute risk reduction; 95% CI: 95% confidence Interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; NA: not applicable; NNT: number needed to treat; NR: not reported; NYHA: New York Heart Association. Table based on data from references #51-54.

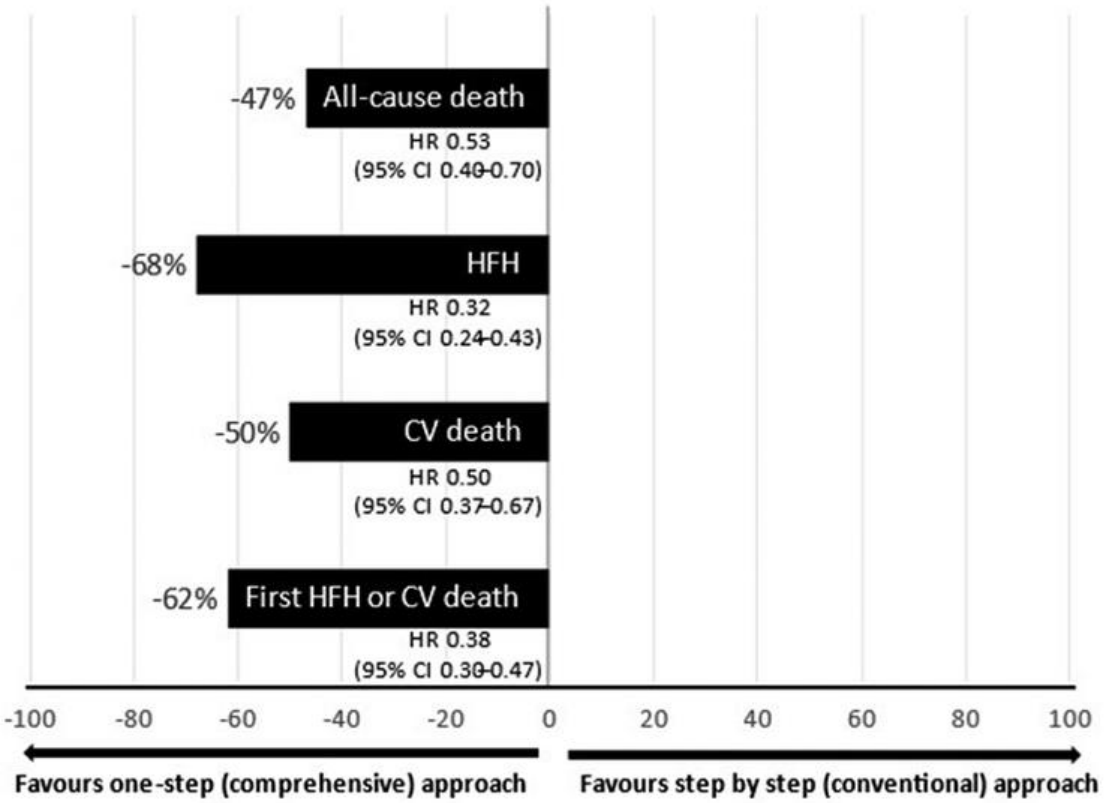

Figure 2. Benefits of the one-step approach vs the step-by-step approach on outcomes in patients with heart failure with reduced ejection fraction. CI: confidence interval; CV: cardiovascular; HFH: heart failure–related hospitalization; HR: hazard ratio.Figure based on data from reference #55.

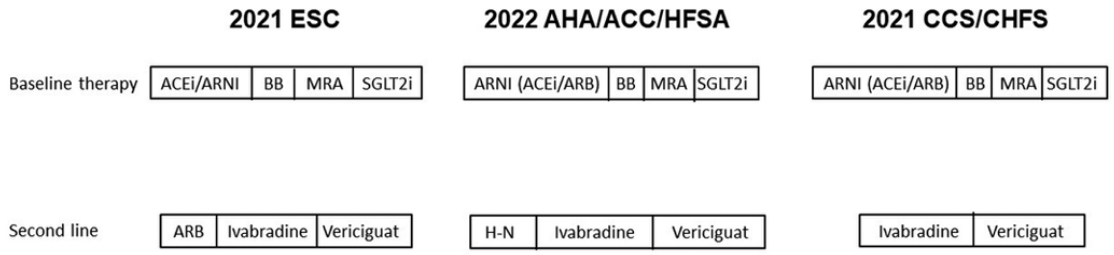

Figure 3. Recommendations from international guidelines on medical treatment of patients with heart failure and reduced ejection fraction.

ACC: American College of Cardiology; ACEi: angiotensin-converting enzyme inhibitor; AHA: American Heart Association; ARB: angiotensin-receptor blocker; ARNI: angiotensin receptor- neprilysin Inhibitor; BB: beta blocker; CCS: Canadian Cardiovascular Society; CHFS: Canadian Heart Failure Society; ESC: European Society of Cardiology; HFSA: Heart Failure Society of America; H-N: Hydralazine/isosorbide dinitrate; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose cotransporter-2.Figure based on data from references #12-14.

Table 2. General recommendations of the 2021 ESC HF guidelines with respect to medical treatment of patients with HF and reduced left ventricular ejection fraction.

Treatment		Indication
Baseline therapy	ACEi (IA) or sacubitril/valsartan [preferred] (IB)	To reduce the risk of HF hospitalization and death
	Beta blockers (IA)	
	MRA (IA)	
	SGLT2 inhibitors (IA)	
Second-line therapy	Vericiguat (IIbB)	If the patient remains symptomatic, if worsening of HF, to reduce the risk of HF-related hospitalization or CV death
	Ivabradine (IIaB/C)	If the patient remains symptomatic, in sinus rhythm, >70 bpm, with (B) or without (C) beta blockers, to reduce the risk of HF-related hospitalization or CV death
	ARB (IB)	If ACEi or sacubitril/valsartan cannot be taken, to reduce the risk of HF-related hospitalization or CV death

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CV: cardiovascular; ESC: European Society of Cardiology; HF: heart failure; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose cotransporter-2.

Table based on data taken from reference #12.

Table 3. Impact of guided HF therapy on blood pressure, heart rate, potassium levels, and renal function and potential side effects. Recommendations on guided HF therapy in different clinical situations.

Drug	Blood pressure	Heart rate	Potassium	Renal function	Recommendations in case of side effects
ACEi/sacubitril-valsartan/ARB	↓	-	↑	↓	- If symptomatic hypotension, reduce/avoid hypotensive drugs without positive impact on outcomes. Evaluate volemic status/need for diuretics. - Renal function: • ACEi/ARB: - Possible impairment (an increase in creatinine of up to 50% above baseline, or <3 mg/ dL/eGFR <25 mL/min/1.73 m^2 is acceptable). - Stop ACEi/ARB, if creatinine increases by >100% or >3.5 mg/dL/eGFR <20 mL/min/ 1.73 m^2. - Stop concomitant nephrotoxic drugs (i.e. NSAIDs) • ARNI: - Possible impairment (acceptable up to ≤eGFR 30 mL/min/1.73 m^2). - If eGFR <30 mL/min/1.73 m^2, stop ARNI. - Stop concomitant nephrotoxic drugs (i.e. NSAIDs) - Potassium: - Possible increase (acceptable up to ≤5.5 mmol/L). - If potassium rises >5.5 mmol/L, stop ACEi/ARB/ARNI.

					- If potassium rises excessively, stop nephrotoxic drugs, potassium supplements, and retaining agents (triamterene, amiloride).
Beta blockers	↓	↓	-	-	- If symptomatic hypotension, reduce/avoid hypotensive drugs without positive impact on outcomes. Evaluate volemic status/need for diuretics. - If congestion increases, adjust diuretics or reduce dose of beta blockers - If marked fatigue, reduce dose of beta blockers - If heart rate <50 bpm and/or worsening of symptoms, consider the need for other heart rate– slowing drugs (i.e. ivabradine, digoxin, amiodarone) and/or consider reducing dose of beta blockers.
MRA	-/↓	-	↑	↓	- Renal function: - Possible impairment. - Reduce the dose if creatinine rises to 2.5 mg/dL/eGFR <30 mL/min/1.73 m^2. - Stop MRA if creatinine increases to >3.5 mg/dL/eGFR <20 mL/min/1.73 m^2. - Stop concomitant nephrotoxic drugs (i.e. NSAIDs) - Potassium: - Possible increase - Reduce the dose if potassium rises >5.5 mmol/L. - Stop MRA, if potassium rises >6.0 mmol/L. - If potassium rises excessively, stop nephrotoxic drugs, potassium supplements or retaining agents (triamterene, amiloride).
SGLT-2 inhibitors	-/↓	-	-	-/↑	- Monitor fluid balance and blood pressure and adjust diuretic dose, if necessary. - Possible slight and transitory impairment of renal function when starting treatment, but renal function is preserved during the long-term follow-up - Monitor for hypoglycemia, particularly in the case of concomitant treatment with

					insulin and/ or sulfonylurea (reduce the dose of concomitant therapy if required) - Monitor symptoms and signs of genitourinary infections.
Ivabradine	-	↓	-	-	- If heart rate <50 bpm and/or bradycardia symptoms, consider the need for other heart rate– slowing drugs (i.e. digoxin, amiodarone) and/or consider reducing dose of ivabradine. - If persistent/permanent atrial fibrillation, stop ivabradine (until sinus rhythm is restored). - If symptomatic visual phenomena persist, consider reducing/stopping ivabradine.
Vericiguat	-/↓	-	-	-	- If side effects occur (symptomatic hypotension or systolic blood pressure <90 mmHg), consider reducing/stopping vericiguat.

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; MRA: mineralocorticoid receptor antagonist; NSAIDs: nonsteroidal anti-inflammatory drugs; SGLT2: sodium-glucose cotransporter-2.

Table based on data from references #12-14,64–66.

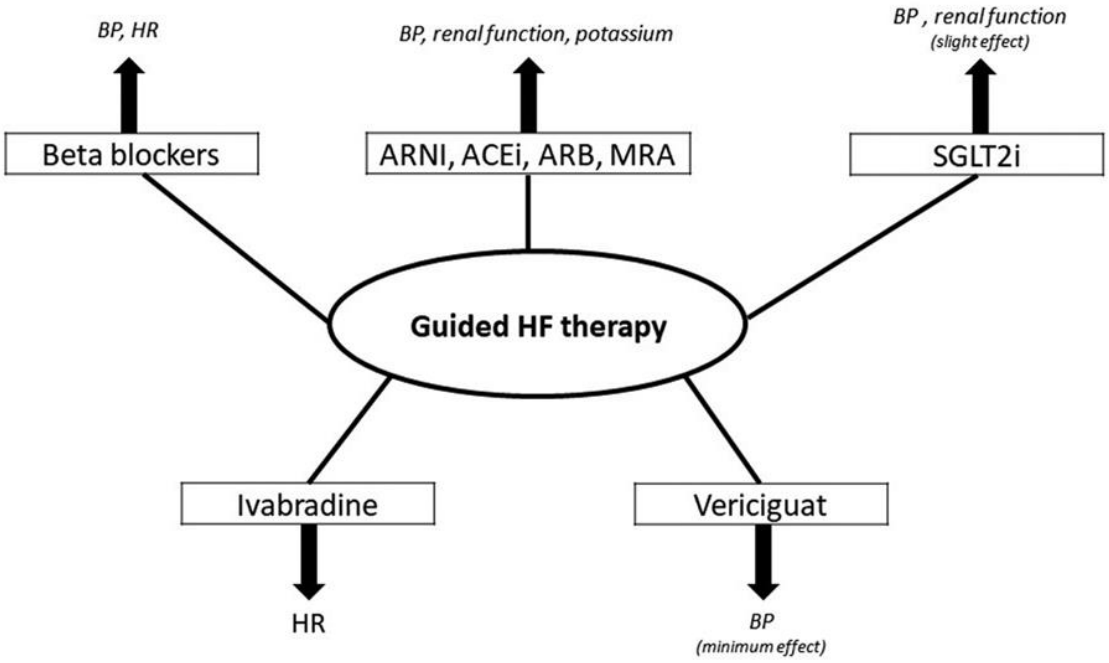

Figure 4. Parameters to be considered for HF drugs monitoring.

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; ARNI: angiotensin receptor-neprilysin Inhibitor; BP: blood pressure; HR: heart rate; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose cotransporter-2 inhibitors.Figure based on data from references #12-14,64–66.

Table 4. Use of guided HF therapy according to clinical characteristics.

Clinical condition	First approach	Following visits

Normal-mild impairment of BP/HR/RF/K	• ACEi/ARNI (preferred)
	• BB
	• MRA
	• SGLT-2 inhibitors
		• If patient remains symptomatic:
		  • Vericiguat (worsening HF/previous HFH)
		  • Ivabradine (sinus rhythm, HR >70 bpm)
		• ARB, if ACEi or ARNI cannot be used

Low BP	• MRA • SGLT-2 inhibitors • Vericiguat (worsening HF/previous HFH)* • Ivabradine (sinus rhythm, HR >70 bpm)	• If BP increases, consider adding ACEi/ARNI (preferred) and BB
Low HR	• ACEi/ARNI (preferred) • MRA • SGLT-2 inhibitors	• If patient remains symptomatic: vericiguat (worsening HF/previous HFH) • If HR increases (rule out HF decompensation), consider adding BB
Low BP and low HR	• MRA • SGLT-2 inhibitors • Vericiguat (worsening HF/previous HFH)*	• If BP increases, consider adding ACEi/ARNI (preferred) and BB • If HR increases (rule out HF decompensation), consider adding BB
High K	• BB • SGLT-2 inhibitors	• If patient remains symptomatic, ivabradine (sinus rhythm, HR >70 bpm)

	• Vericiguat (worsening HF/previous HFH)	• Use K binders (i.e. patiromer sorbitex calcium, sodium zirconium cyclosilicate) and consider RAAS inhibitors if K levels normalize

CKD (eGFR >30 mL/min/ 1.73 m^2)	• ACEi/ARNI (preferred)
	• BB
	• MRA
	• SGLT-2 inhibitors
		• If patient remains symptomatic:
		  • Vericiguat (worsening HF/previous HFH)
		  • Ivabradine (sinus rhythm, HR >70 bpm)
		• ARB, if ACEi or ARNI cannot be used

CKD (eGFR <30 mL/min/ 1.73 m^2)	• BB • SGLT-2 inhibitors • Vericiguat (worsening HF/previous HFH)	• If patient remains symptomatic, ivabradine (sinus rhythm, HR >70 bpm)
Atrial fibrillation	• ACEi/ARNI (preferred) • BB • MRA • SGLT-2 inhibitors • Anticoagulation	• If patient remains symptomatic: • Vericiguat (worsening HF/previous HFH) • If HR remains uncontrolled despite BB: • Digoxin • ARB, if ACEi or ARNI cannot be used

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; ARNI: angiotensin receptor-neprilysin Inhibitor; BB: beta blockers; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HFH: HF-related hospitalization; HR: heart rate; K: potassium; MRA: mineralocorticoid receptor antagonist; RF: renal function; SGLT2: sodium-glucose cotransporter-2. Treatment with vericiguat should not be initiated in patients with systolic BP <100 mmHg.

Table based on data from references #12-14,64–66.

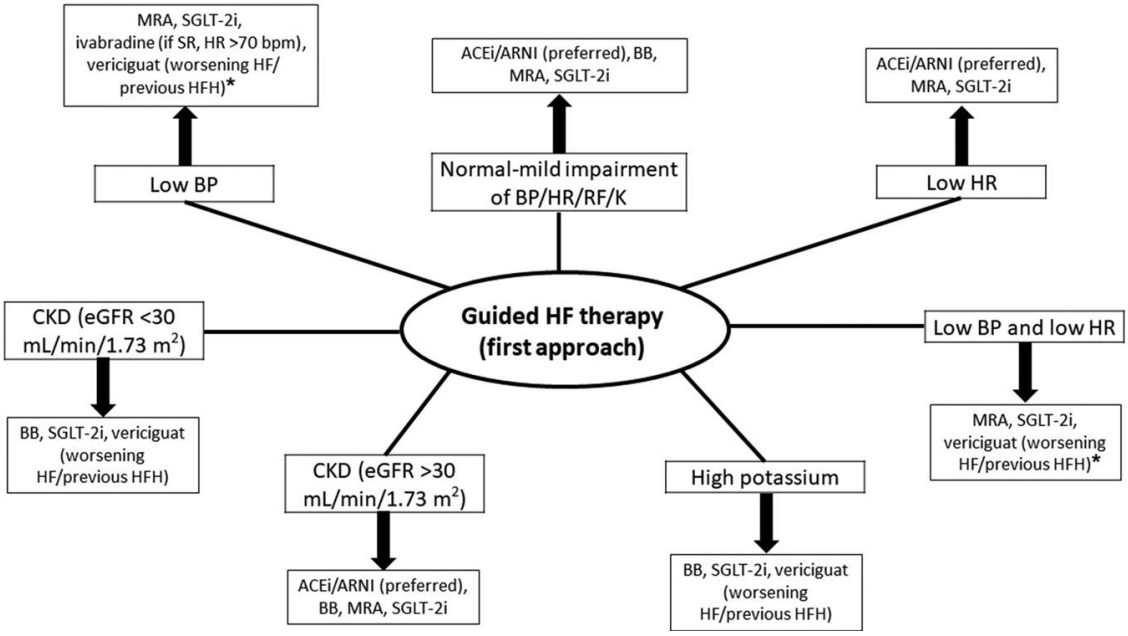

Figure 5. Initial approach of guided HF therapy according to clinical characteristics.

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; ARNI: angiotensin receptor-neprilysin Inhibitor; BB: beta blockers; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HFH: HF-related hospitalization; HR: heart rate; K: potassium; MRA: mineralocorticoid receptor antagonist; RF: renal function; SGLT2i: sodium-glucose cotransporter-2 inhibitors. *Treatment with vericiguat should not be initiated in patients with systolic BP <100 mmHg. Figure based on data from references #12-14,64–66.