Patient Preference and Adherence

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REVIEW

Optimization of Patient Pathway in Heart Failure with Reduced Ejection Fraction and Worsening Heart Failure. Role of Vericiguat

José Ramón González-Juanatey[1], Josep Comín-Colet[2], Domingo Pascual Figal[3], Antoni Bayes-Genis[4], Jose Maria Cepeda[5], José M García-Pinilla[6,7], Antonio García-Quintana[8], Luis Manzano[9], Jose Luis Zamorano[10]

[1]Cardiology Department, Hospital Clínico Universitario Santiago de Compostela, Centro de investigación Biomédica en Red Enfermedades Cardiovasculares (CIBERCV), Santiago de Compostela, Spain; [2]Cardiology Department, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain; [3]Cardiology Department, Hospital Virgen de la Arrixaca, University of Murcia, Murcia, Spain; [4]Cardiology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [5]Department of Internal Medicine, Hospital Vega Baja, Orihuela, Alicante, Spain; [6]Cardiology Department, Hospital Universitario Virgen de la Victoria, IBIMA, Málaga, Spain; [7]Department of Medicine and Dermatology, Universidad de Málaga, Málaga, Spain; [8]Cardiology Department, Hospital Universitario de Gran Canaria Doctor Negrín, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [9]Department of Internal Medicine, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Universidad de Alcalá, Madrid, Spain; [10]Cardiology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain

Correspondence: José Ramón González-Juanatey, Email Jose.Ramon.Gonzalez.Juanatey@sergas.es

Abstract: Heart failure (HF) is a progressive condition with periods of apparent stability and repeated worsening HF events. Over time, unless optimization of HF treatment, worsening HF events become more frequent and patients enter into a cycle of recurrent events with high morbidity and mortality. In patients with HF there is an activation of deleterious neurohormonal pathways, such as the renin angiotensin aldosterone system and the sympathetic system, and an inhibition of protective pathways, including natriuretic peptides and guanylate cyclase. Therefore, HF burden can be reduced only through a holistic approach that targets all neurohormonal systems. In this context, vericiguat may play a key role, as it is the only HF drug that activates the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate system. On the other hand, it has been described relevant disparities in the management of HF population. Consequently, it is necessary to homogenize the management of these patients, through an integrated patient-care pathway that should be adapted at the local level. In this context, the development of new technologies (ie, video call, specific platforms, remote control devices, etc.) may be very helpful. In this manuscript, a multidisciplinary group of experts analyzed the current evidence and shared their own experience to provide some recommendations about the therapeutic optimization of patients with recent worsening HF, with a particular focus on vericiguat, and also about how the integrated patient-care pathway should be performed.

Keywords: heart failure, worsening heart failure, patient-care pathway, vericiguat

Introduction

Heart failure (HF) is very common in clinical practice and it is associated with high morbidity and mortality. The HFA Atlas survey showed that in Europe in 2018–2019, although with relevant differences between countries, the incidence of HF was 3.20 cases per 1000 person-years, the HF prevalence was 17.20 cases per 1000 people, and the number of HF hospitalizations was 2671 per million people annually, with a length of hospital stay of 8.50 days.[1] Of note, the RECALCAR project showed that in Spain, between 2007 and 2019, whereas the crude mortality rate during hospitalization for acute coronary syndrome has progressively decreased over time, this has remained stable for HF.[2,3] On the other hand, among patients with acute HF admission, the 15- and 30-day readmission rates due to cardiovascular reasons are high (7% and 14%, respectively),[4] although these numbers could be even greater.[5] In addition, a large portion of the annual health-care budget is devoted to HF patients, with unplanned hospitalization representing the main source of

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healthcare-related expenditure (around 75%), and only a small proportion of total costs corresponding to medication costs (7%).[6,7]

Worsening Heart Failure (WHF): Relevance and Needs

HF is a progressive condition that punctuates periods of apparent stability with repeated WHF events. WHF includes all inpatient or outpatient decompensation events requiring intravenous diuretic therapy.[8] Over time, unless optimization of HF treatment, WHF events become more frequent and patients enter into a cycle of recurrent events.[9] This is very relevant, as each HF hospitalization is not only associated with a significant reduction of quality of life, but also with an increased risk of death that raises with each HF hospitalization.[10,11] In fact, WHF is associated with a four-fold increase in 1-year mortality risk compared with chronic HF, from 6% to 28%.[12] However, the risk of cardiovascular death or HF hospitalization is highest in the early phase after hospitalization. For example, a substudy of the PARADIGM-HF trial showed that compared with patients with no prior hospitalization, whereas the risk of cardiovascular death or HF hospitalization was 26% higher in patients with a prior HF hospitalization >12 months, this was a 46% greater in those with a recent hospitalization (<6 months).[13]

As a result, it is necessary to optimize the management of patients with HF, with the early use of disease-modifying treatment.[14] However, it has been described relevant disparities regarding mortality and readmission rates among patients hospitalized for HF between those specialties that attend the HF patient (ie, cardiology, internal medicine, etc.), mainly due to differences in the clinical profile and management of these patients, and also between different Autonomous Communities in Spain.[2,3] In this context, it is important to stratify and identify those patients at high risk of decompensation, particularly those with a recent WHF episode in order to provide a better approach through an integrated patient-care pathway.

A multidisciplinary group of experts about the management of patients with HF analyzed the current evidence and shared their own experience to provide some recommendations about how the integrated patient-care pathway should be performed. In addition, this group of experts analyzed the role of vericiguat in the management of patients with recent WHF.

Patient Pathway and Health Care Transition

After an acute HF decompensation, which can be either in an outpatient or in patient setting (ie, hospitalization, emergency department, outpatient clinic/day hospital), the patient pathway can be very heterogenous, as it currently depends on the specialist that treat the patient and also the specific health-care system in which the patient is attended.[15–17] Consequently, it is necessary to homogenize the management of these patients. The main components of the health-care organization among patients with WHF should include all settings in which the patients can be assisted (ie, hospitalization, emergency department, day hospital, office clinic), in order to optimize the management of the patient flow. Only through a multidisciplinary (ie, physicians and nurses) and patient-centered approach, an adequate continuity of care can be assured, reducing readmissions and further complications. This approach should focus on the early intervention during all phases of the patient´s journey, including the inpatient phase, discharge planning, early post-discharge visits and structured follow-up.[18,19] Remarkably, this should be adapted to the local health-care system, considering the actual material and human resources available. In addition, specific indicators should be established to analyze the impact of the actions developed at the local level[20–22] (Figure 1).

When the patient presents with WHF and require intravenous diuretics, the patient can be attended in the day hospital, emergency department or may require hospitalization, according to the severity of the decompensation. After stabilization, the discharge process and transition of care should be adequately organized not only from a global level, but mainly from a local point of view. In this context, the characteristics of the discharge report have to be well defined, indicating the diagnostic and therapeutic procedures performed during the decompensation, as well as the therapeutic targets (ie, blood pressure, heart rate, etc.). Additionally, the therapeutic plan, as well as the follow-up visits should also be included. During the transition of care, an appropriate communication and integration between different health-care providers, including physicians (internal medicine, cardiology, primary care, etc.), nurse and patients/caregivers should be promoted.[22] In this context, the European guidelines recommend that before discharge, persistent signs of congestion

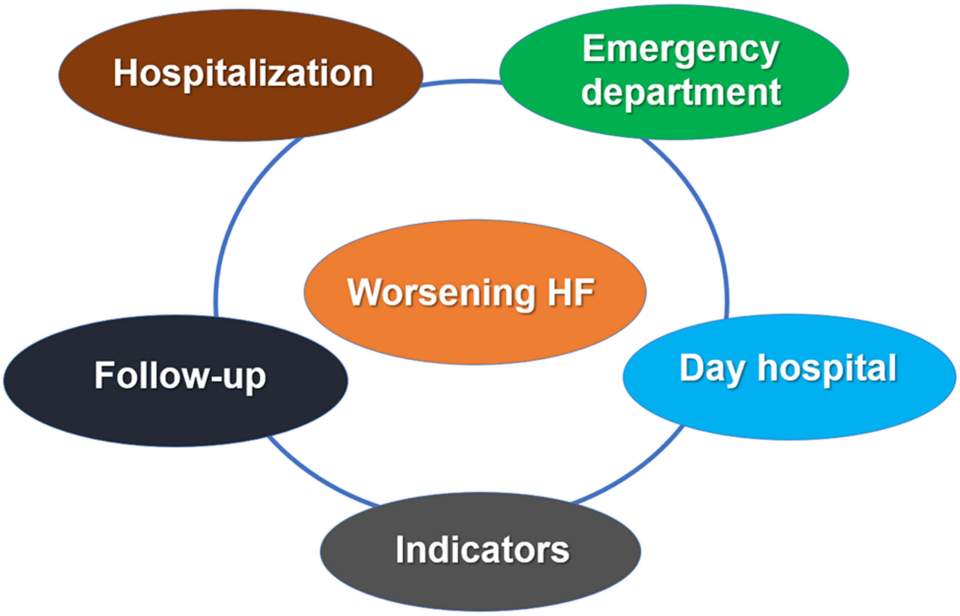


Figure 1 Components of the health care organization.

should be excluded and, when possible, optimization of oral treatment (disease-modifying therapies) should start during hospitalization or at least at early post-discharge phase. In addition, an early follow-up visit is recommended at 1–2 weeks after discharge.[14] However, the Spanish Society of Cardiology considers that it would be desirable to have a first telephonic contact <24–48 hours after discharge with nurse and an office visit with the primary care physician and the specialist (cardiology or internal medicine), within the first 7–10 days and 30 days after discharge, respectively.[22]

In addition, telemedicine offers a unique opportunity that facilitates the transition and continuity of care of patients with HF. There are different formats of telemedicine consultation that can be used in this population, according to the specific characteristics of the population and the material and human resources that are available in each sanitary area. These formats may include telephone, video call, specific platforms, and remote control devices. These formats are fully complementary.[23–25] In fact, different studies have demonstrated that within the comprehensive management of patients with HF, the addition of telemedicine may result in better outcomes, including the prevention of further HF events and reduction of costs, regardless frailty status of patients.[26–31] Therefore, both, telemedicine and face-to-face visits are useful tools that can be adapted to the need that the patient require at each moment.[23–25] Additionally, electronic consultations are an excellent instrument that facilitates the communication between different health-care providers, promoting the comprehensive management of patients with HF.

Finally, it is necessary to develop specific quality indicators of the process and to analyze the health results to determine areas of improvement in order to optimize the patient pathway, with a particular focus on the transition and continuity of care and the early implementation and uptitration of disease-modifying therapies.[22] In summary, to increase the early use of guideline-directed medical therapies, it is necessary the development of multidisciplinary HF management programs, locally adapted, through the use of electronic patient awareness tools, telehealth and electronic medical interventions for providers.[32] Figures 2 and 3 represent general examples of the health-care pathways of the patients with HF, according to the settings they are attended.

Vericiguat and the VICTORIA Trial

In patients with HF there is an activation of deleterious neurohormonal pathways, such as the renin angiotensin aldosterone system (RAAS) and the sympathetic system, and an inhibition of some protective pathways, including the systems of natriuretic peptides and guanylate cyclase. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and angiotensin II and neprilysin antagonists (ARNI) effectively inhibit RAAS, whereas beta

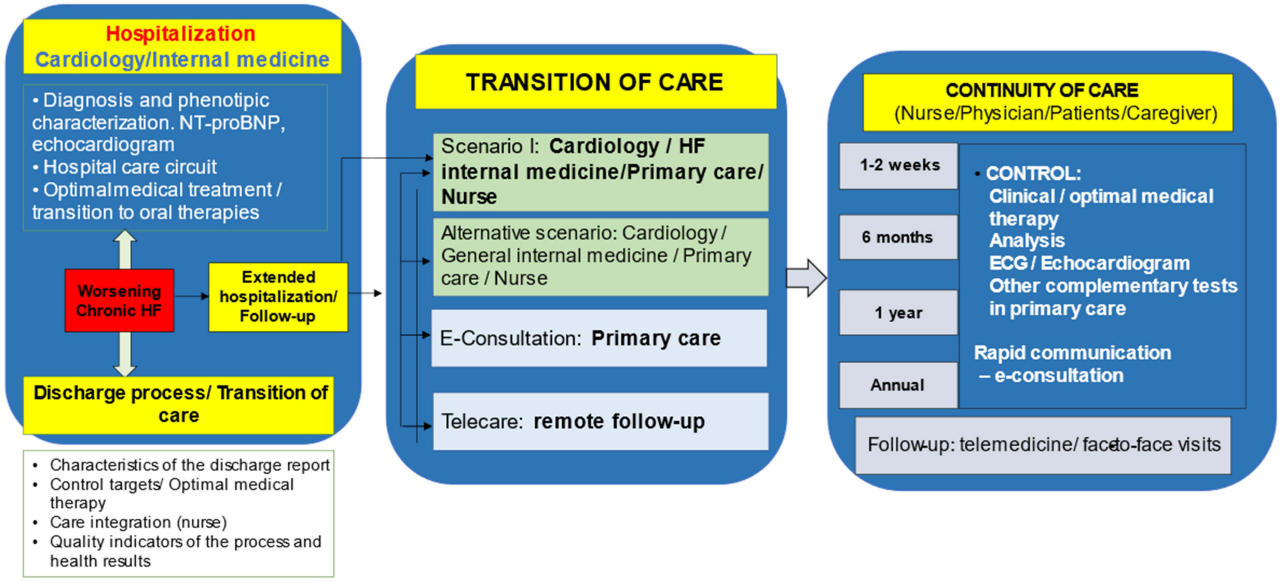


Figure 2 Health care pathway of a patient hospitalized with WHF.
Abbreviations: HF, heart failure; ECG, electrocardiogram; WHF, worsening heart failure.

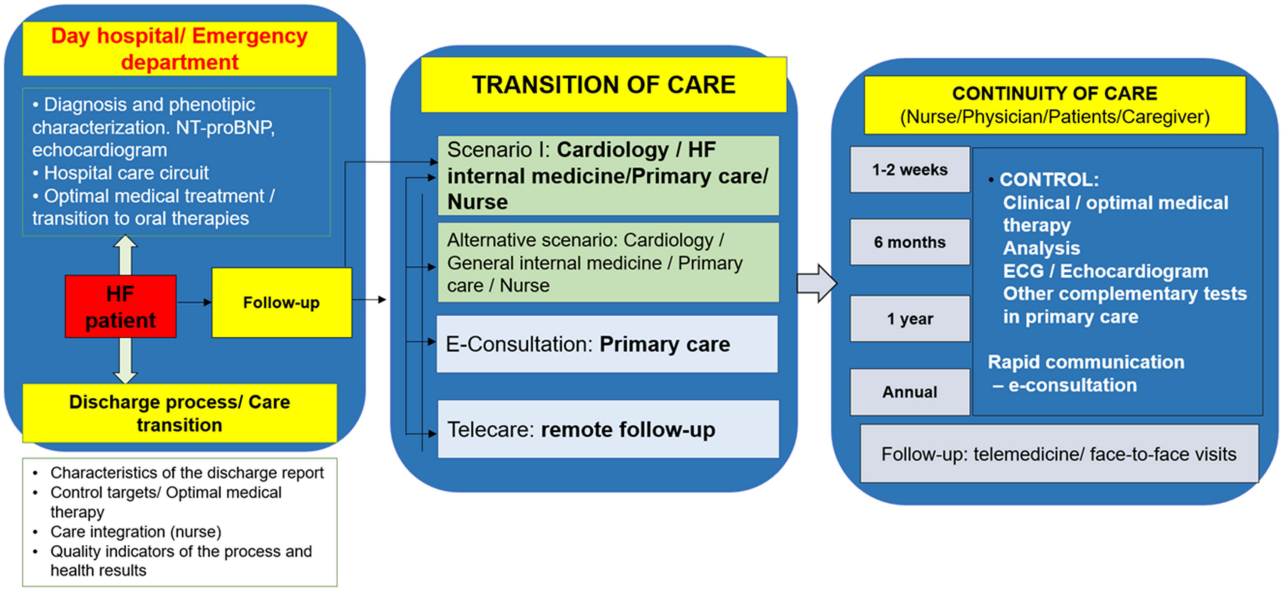


Figure 3 Health care pathway of a patient with WHF firstly attended in the day hospital or the emergency department.
Abbreviations: HF, heart failure; ECG, electrocardiogram; WHF, worsening heart failure.

blockers the sympathetic system. In contrast, ARNI stimulates the natriuretic peptide system through the neprilysin inhibition. Additionally, although the main mechanisms are not well known, the sodium-glucose co-transporter 2 inhibitors (SGLT2i) provide a positive impact in patients of HF, with a reduction of cardiovascular events. However, none of the previous HF therapies acts on the guanylate cyclase system.[33–36]

Remarkably, oxidative stress and endothelial dysfunction lead to a decreased activity of the nitric oxide and soluble guanylate cyclase and ultimately, to a reduction of the production and activity of the cyclic guanosine monophosphate (cGMP). The impairment of this system is associated with important negative effects on the cardiovascular and renal systems. Vericiguat is an oral soluble guanylate cyclase stimulator that may reverse, or at least improve these alterations, in the heart, by reducing myocardial stiffening, fibrosis, and ventricular hypertrophy and remodeling, in the kidneys, by

decreasing fibrosis and improving renal blood flow and in the blood vessels, by reducing vasoconstriction and enhancing endothelial function.[37,38] Therefore, to actually reduce HF burden, it is necessary to provide a complete approach that targets all the different neurohormonal systems, particularly in those patients at high risk, such as those with a recent WHF episode.[39] In this context, vericiguat provides important benefits, as the VICTORIA trial has demonstrated.[40]

Victoria was a Phase 3, randomized, double-blind, placebo-controlled trial that included 5050 patients with symptomatic chronic HF, a left ventricular ejection fraction <45%, elevated natriuretic peptide levels and evidence of WHF, defined as HF hospitalization within the 6 months before randomization or receiving intravenous diuretic therapy, without hospitalization, within the previous 3 months. Patients received vericiguat (target dose of 10 mg once daily) or placebo, in addition to standard therapy. The majority of patients were in NYHA functional class II (59%) or III (40%), 67% and 17% had been hospitalized within 3 months and 3–6 months before randomization, respectively, and 16% required intravenous diuretic for HF, without hospitalization.[40]

In the VICTORIA trial, treatment with vericiguat was associated with a significant reduction in the risk of the primary outcome, the composite of death from cardiovascular causes or first HF hospitalization by 10% (HR 0.90; 95% CI 0.82–0.98) after a median follow-up of 10.8 months. In addition, vericiguat significantly reduced total HF hospitalizations by 9% (HR 0.91; 95% CI 0.84–0.99) and the composite of death from any cause or HF hospitalization by 10% (HR 0.90; 95% CI 0.83–0.98).[40] These results were consistent regardless of the previous use of HF treatment, renal function, or index event, and were particularly effective in those patients with NT-proBNP levels <8000 pg/mL.[40–44] In addition, vericiguat was very well tolerated, with similar rates of adverse events and serious adverse events than placebo. With regard to systolic blood pressure, there was a discrete decrease with vericiguat that occurred in the first weeks of treatment before returning to baseline, but rates of symptomatic hypotension or syncope were similar between groups. Of note, vericiguat did not modify the renal function or sodium or potassium levels.[40]

Vericiguat in the Comprehensive Pharmacological Management of WHF

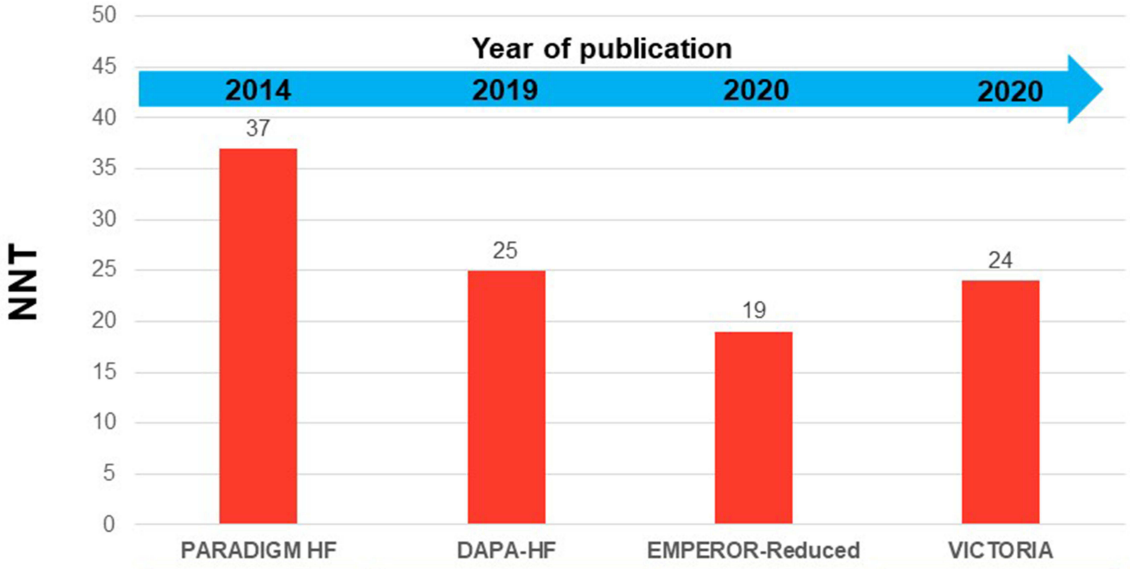
Vericiguat in Perspective of Other Contemporary Clinical Trials

To actually understand the relevance of the results of the VICTORIA trial, it is important to know the design and the results of the more contemporary clinical trials (Figure 4).[40,45–47] The PARADIGM-HF trial included patients with symptomatic HF with reduced ejection fraction (≤35%), 71% in NYHA functional class II, median NT-proBNP 1608 pg/mL, and 31% hospitalized for HF within the 6 months before inclusion. Compared with placebo, sacubitril/valsartan reduced the risk of the primary endpoint (first HF hospitalization or cardiovascular death) by 20%.[45] The DAPA-HF included patients with symptomatic HF with reduced ejection fraction (≤40%), 68% in NYHA functional class II, median NT-proBNP 1437 pg/mL and 16% hospitalized for HF within the 6 months before inclusion. Compared with placebo, dapagliflozin reduced the risk of the primary endpoint (WHF or cardiovascular death) by 26%.[46] The EMPEROR-Reduced included patients with symptomatic HF with reduced ejection fraction (≤40%), 75% in NYHA functional class II, median NT-proBNP 1906 pg/mL. Compared with placebo, empagliflozin reduced the risk of the primary endpoint (first HF hospitalization or cardiovascular death) by 25%.[47] In the VICTORIA trial, 59% of patients were in NYHA functional class II, median NT-proBNP was 2816 pg/mL and 84% hospitalized for HF within the 6 months before inclusion. Compared with placebo, vericiguat reduced the risk of the primary endpoint (first HF hospitalization or cardiovascular death) by 10%.[40]

Therefore, there are important differences regarding inclusion criteria and baseline clinical characteristics. As a result, direct comparisons cannot be performed between these studies. Despite that, absolute differences between these contemporary studies were very close (NNT ranged from 19 to 37).[40,45–47] However, it is important to emphasize that only the VICTORIA trial specifically analyzed those patients with WHF as inclusion criteria.

Contemporary Guideline-Directed Medical Therapies

International guidelines recommend that unless contraindicated, patients with HF with reduced ejection fraction should be treated with a RAAS inhibitor, preferably ARNI, a beta blocker, a mineralocorticoid receptor antagonist (MRA) and a SGLT2i to reduce the risk of HF hospitalization and death.[14,48,49] These drugs should be prescribed as early as possible, trying to achieve the target doses if tolerated.[39]



	PARADIGM HF Sacubitril/valsartan	DAPA-HF Dapagliflozin	EMPEROR-Reduced Empagliflozin	VICTORIA Vericiguat
Age, years	64	66	67	68
NYHA functional class III-IV, %	25	32	25	41
LVEF, %	≤35	≤40	≤40	≤45
NT-proBNP (median), pg/ml	1,608	1,437	1,906	2,816
HFH <3 months, %	19	8	NR	67
HFH <6 months, %	31	16	NA	84
SOC (control group)				
ACEi/ARB, %	100	83	69	74
ARNI, %	0	11	21	15
BB, %	93	96	95	93
MRA, %	57	71	73	71
Follow-up, months (median)	27	18	16	11
Primary endpoint	First HFH or CV death	HF worsening or CV death	First HFH or CV death	First HFH or CV death
HR	0.80	0.74	0.75	0.90
ARR, %	2.7	4.0	5.2	4.2
NNT	37	25	19	24
P	<0.001	<0.001	<0.001	0.02

Figure 4 Baseline clinical characteristics and results of the primary outcome in the PARADIGM-HF, DAPA-HF, EMPEROR-Reduced and Victoria trials.
Note: Figure performed with data from these studies.[40,45–47]
Abbreviations: AAR, absolute risk reduction; ACEi, angiotensin-converting–enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, Angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HR, Hazard Ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid antagonist; NNT, Number of patients Needed to Treat; NYHA, New York Heart Association; SOC, standard of care.

In the light of the evidences with vericiguat, mainly provided from the VICTORIA trial, international guidelines are in general very homogeneous in their recommendations, and they state that vericiguat may be considered to reduce HF hospitalization and cardiovascular death in patients with HF with reduced ejection fraction and recent WHF already on maximum tolerated optimal HF therapy (Table 1).[14,48,49] As the pathogenesis of HF is complex, with the implication of numerous neurohormonal systems, a holistic approach is mandatory to reduce the morbidity and mortality among patients with HF. In this context, vericiguat may add benefits over the rest of disease-modifying therapies.[50] Thus, in a systematic network meta-analysis, of 75 relevant trials representing 95,444 participants, the combination that most effectively reduced all-cause death was ARNI, beta blockers, MRA, and SGLT2i, followed by ARNI, beta blockers, MRA and vericiguat. The combination of ARNI, beta blockers, MRA and vericiguat significantly reduced the risk of cardiovascular death and first HF hospitalization by 57% and all-cause mortality by 59%.[51] Therefore, vericiguat represents an added value in the management of patients with HF with reduced ejection fraction.

On the other hand, as guidelines recommend, evidence-based oral medical treatment should be administered as soon as possible, preferably before discharge and uptitration of disease-modifying therapies should start during the early post-discharge phase.[14,48,49] A HF therapeutic optimization pathway of patients with recent WHF episode is presented in Figure 5. WHF includes not only those patients with hospitalization for HF, but also those that require intravenous

Table 1 Recommendations of International Guidelines and Expert Consensus About the Use of Vericiguat in Patients with Heart Failure with Reduced Ejection Fraction

Guidelines		Expert Consensus
Recommendation	**Class (Evidence)**	**Symptomatic Patients with HFrEF and Previous WHF:**
AHA/ACC/HFSA2022 Vericiguat may be considered to reduce HFH and CV death in selected high-risk patients with HFrEF and **recent WHF** already on optimal HF therapy	2b (B–R*)	• During hospitalization, at discharge or early discharge phase (patients with previous optimal medical therapy). • Previous outpatient or inpatient decompensation. • In all patients with optimal medical HF therapy that remain symptomatic. • Patients at high risk of HF decompensation. • Vericiguat could facilitate the initiation/ uptitration of other HF drugs. • Better taking all HF drugs rather than delaying the addition of some HF drug because of uptitration of other one.
ESC 2021 Vericiguat may be considered in patients in symptomatic patients who have had **WHF** despite optimal HF treatment to reduce the risk of CV mortality or HFH	IIb (B)	
CCS/CHFS 2021 Vericiguat may be considered in addition to optimal HF therapies for HFrEF patients with **worsening symptoms** and HFH in the past 6 months, to reduce the risk of subsequent HFH	Conditional[#] (moderate quality)	

Notes: *Level of evidence B from a randomized trial; [#]A conditional recommendation is provided until vericiguat is approved for this indication in Canada. Table performed with data from references[#].[14,48,49]

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; CHFS, Canadian Heart Failure Society; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; WHF, worsening heart failure.

diuretics for decompensated HF, either treated in the emergency department or in an outpatient setting (day hospital). In addition, two algorithms according to whether patients have been previously treated with oral disease-modifying therapies are presented. Of note, the initial prescription of these drugs is mandatory, but also uptitration during the

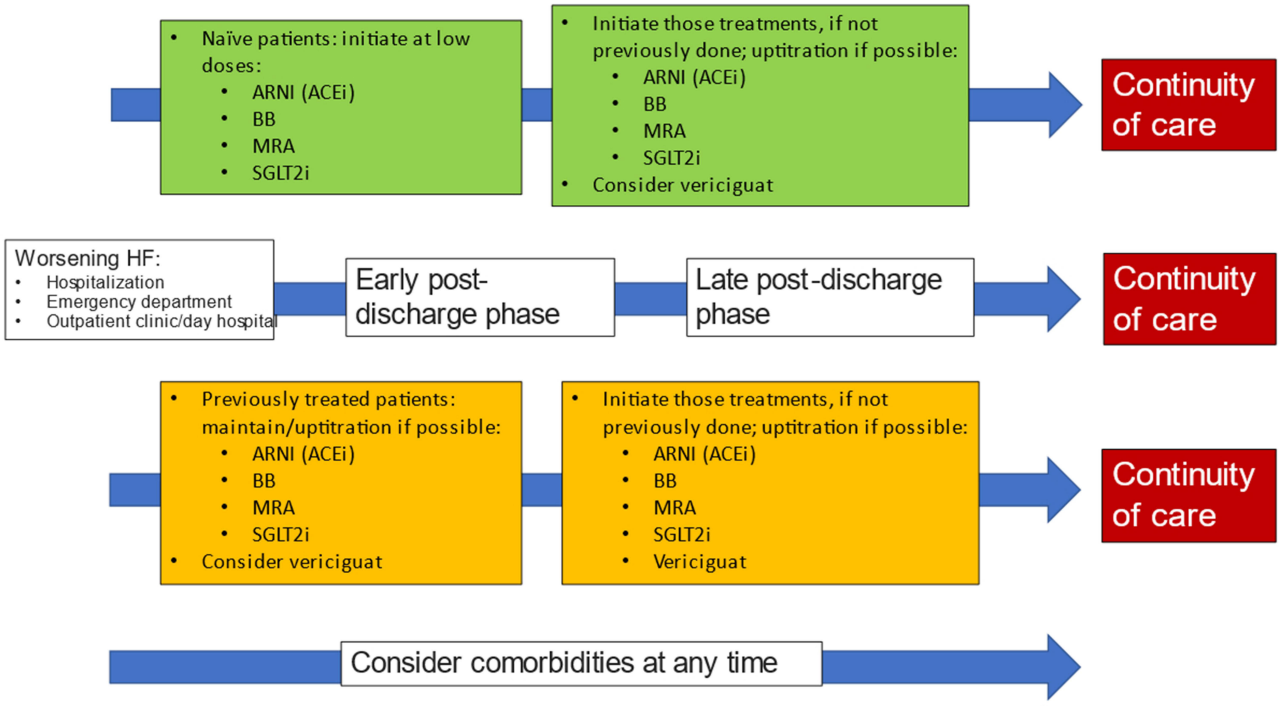


Figure 5 Therapeutic optimization of patients with recent WHF episode.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARNI, angiotensin II and neprilysin antagonists; BB, beta blockers; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitors; WHF, worsening heart failure.

follow-up. Assuring an adequate continuity of care through an appropriate communication between health-care levels is required.

Adherence and Optimization

A comprehensive pharmacological approach may be limited by side effects/tolerability concerns. A recent systematic review of 37 studies showed that in patients with HF and reduced ejection fraction, the proportion of patients that reached the target doses for ACEi/ARB, ARNI, beta-blockers, and MRA ranged from 4% to 55%, 11% to 87%, 4% to 60%, and 22% to 80%, respectively. Elderly, worsening renal function, hyperkalemia and hypotension were associated with non-use or sub-therapeutic dose.[52] In this context, it is necessary to know the side effects associated with each drug. Thus, ACEi/ARB/ARNI/MRA may cause hypotension, worsening renal function and hyperkalemia, beta blockers may produce symptomatic deterioration, asthenia, bradycardia, or hypotension, and the use of SGLT2i may be associated with an increased risk of genitourinary infections, hypoglycemia, dehydration, hypotension and prerenal renal failure.[14] With regard to vericiguat, no dose adjustment is required according to renal function (avoid if estimated glomerular filtration rate <15 mL/min/1.73 m^2), and has a minimal impact on systolic blood pressure (mean reduction 1–2 mmHg), renal function or electrolytes. In case of symptomatic hypotension or systolic blood pressure <90 mmHg), temporary down-titration or discontinuation is recommended.[53]

To reduce the possibility of adverse events, some parameters according to the type of HF drug, such as blood pressure, heart rate, renal function or potassium, should be monitored for the initiation or uptitration (Table 2).[14] In this context, among patients with HF with reduced ejection fraction, the initiation and uptitration of guideline-directed medications should be individualized according to patient's symptoms, vital signs, tolerance, renal function, electrolytes, and comorbidities. As a result, initiation/uptitration should be performed according to these characteristics, rather than the standard recommended sequence, in order to provide the best and early therapeutic approach in each patient with HF.[14,39,48,49] Despite the recommendations performed by guidelines, we consider that the prescription of vericiguat can be extended to other subgroups of patients, according to their clinical characteristics (Table 1).

Conclusion

The best approach to reduce HF morbidity and mortality is the early implementation of disease-modifying therapies. This is even more important among patients with a recent WHF episode, in which the risk is more marked. As the pathogenesis of HF is complex, with the implication of different neurohormonal systems (ie, RAAS and sympathetic, natriuretic peptides and guanylate cyclase), a holistic approach is mandatory to reduce the morbidity and mortality among patients with HF. In this context, vericiguat may play a key role. On the other hand, in patients with WHF it is necessary to homogenize the management of patients with HF through an integrated patient-care pathway that should be adapted at the local level.

Table 2 Parameters to Be Considered for Initiation/Uptitration of HF Drugs

Drugs	Parameters
Beta blockers	Blood pressure, heart rate, congestive symptoms
ARNI/ACEi/MRA	Blood pressure, renal function, potassium
SGLT2i*	Blood pressure, renal function
Vericiguat	Blood pressure
Ivabradine	Heart rate

Notes: *No uptitration is required. Table performed with data from McDonagh et al.[14]
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARNI, angiotensin II and neprilysin antagonists; BB, beta blockers; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

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