

REVIEW

Vulnerable period in heart failure: a window of opportunity for the optimization of treatment – a statement by Mexican experts

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Abstract

Acute heart failure (HF) is associated with poor prognosis. After the acute event, there is a vulnerable period during which the patient has a marked risk of readmission or death. Therefore, early optimization of treatment is mandatory during the vulnerable period. The objective of this article is to provide recommendations to address the management of patients with HF during the vulnerable period from a practical point of view. A group of Mexican experts met to prepare a consensus document. The vulnerable period, with a duration of up to 6 months after the acute event – either hospitalization, visit to the emergency department or the outpatient clinic/day hospital – represents a real window of opportunity to improve outcomes for these patients. To best individualize the recommendations, the management strategies were divided into three periods (early, intermediate and late vulnerable period), including not only therapeutic options but also evaluation and education. Importantly, the recommendations are addressed to the entire

cardiology team, including physicians and nurses, but also other specialists implicated in the management of these patients. In conclusion, this document represents an opportunity to improve the management of this population at high risk, with the aim of reducing the burden of HF.

Keywords: acute, decompensation, heart failure, treatment, vulnerable period.

Citation

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Introduction

Heart failure (HF) represents a major healthcare problem, reaching epidemic figures worldwide. It has been estimated that more than 60 million individuals experience this condition, with an overall prevalence of 2% in the adult population of developed countries though the prevalence increases with age.¹ HF has a negative impact not only on morbidity and mortality but also on quality of life.² The Olmsted County study showed a mortality of 20% within the first year after diagnosis, with a mean rate of hospitalization of 1.3 per person-years.³ However, because of population growth, ageing and the increasing prevalence of some comorbidities (e.g. hypertension, diabetes and ischaemic heart disease), the absolute number of HF hospitalizations will increase markedly in the coming years.⁴

The natural history of HF is defined by different phases of resolution of symptoms – persistent or worsening HF – that require specific diagnostic and therapeutic approaches.^{2,5} The vulnerable period of HF characterizes a particular period of HF with a high susceptibility to adverse outcomes, including mortality and rehospitalization, therefore representing a window of opportunity to reduce HF burden.⁶

Herein, an update on the vulnerable period of HF with reduced ejection fraction (HFrEF) is provided and recommendations are given regarding the management of HF during this phase. For this purpose, a review was performed of the impact on acute HF on the course of the condition, of the role of acute HF treatment on prognosis, and of management strategies in the early, intermediate and late vulnerable periods of HF to reduce the risk for further events.

Review

Acute HF and its impact on hospitalizations in the natural history of HF

Acute HF can be defined as a cluster of clinical syndromes characterized by symptoms and signs of clinically relevant pulmonary or systemic congestion, with or without data on low cardiac output. Acute HF can present as rapid or gradual onset of symptoms amongst patients with chronic HF (acutely decompensated HF) or as the first diagnosis (de novo HF) and may lead to HF hospitalization or a visit to the emergency department.² According to current guidelines, there are four clinical scenarios of acute HF: acute decompensated HF, acute pulmonary oedema, isolated right ventricular failure and cardiogenic shock.²

In developed countries, acute HF represents the first cause of hospitalization in people aged >65 years, above acute coronary syndromes, cerebrovascular diseases or arrhythmias.^{1,7} Although the pathophysiology of acute HF is highly heterogeneous, each acute episode promotes the development of haemodynamic and structural alterations not only at the cardiovascular level but also in other organs (i.e. kidney or liver), which have a direct negative impact on patient prognosis.⁸ Remarkably, the prognosis worsens with each HF rehospitalization. Thus, life expectancy decreases from 2.5 years after the first HF hospitalization to less than 1 year in those patients with four or more HF hospitalizations.⁹ In addition, the risk of rehospitalization increases after an acute HF episode. In fact, it has been estimated that around one in four patients will be newly hospitalized within the first 30 days after the first event and up to 50% at 60 days.⁹ Moreover, HF-related costs are substantial, with HF hospitalizations being the most important determinant (up to 75–80%).^{4,10}

Many reasons have emerged to try to explain this phenomenon. These causes may include delays in identifying acute HF and prescription of the appropriate treatment as well as the discharge of some patients who remain with congestive symptoms, the marginal impact of acute HF treatment on medium-term and long-term prognosis, and the lack of a specific and structured protocol after discharge. Therefore, it is necessary to improve the early identification and management of acute HF to increase the implementation of guideline recommendations, to define when is the best moment for the safe discharge of patients and, finally, to enhance communication between the healthcare team to achieve an adequate transition to the outpatient setting.^{6,11–16}

Treatments for acute HF and impact on medium-term and long-term prognosis

In addition to controlling symptoms, the therapeutic targets of HF include improving prognosis and reducing HF hospitalizations.¹⁷ Different drugs have been used for the management of patients with acute HF, including intravenous diuretics, vasodilators, inotropes, inodilators and, more recently, mechanical circulation support for extreme cases.^{2,17} Unfortunately, their impact on prognosis beyond hospitalization remains uncertain (Table 1).^{18–27}

In the VMAC (Vasodilatation in the Management of Acute CHF) study, intravenous nesiritide, a recombinant form of the 32-amino acid human B-type natriuretic peptide, improved haemodynamic function and some self-reported symptoms compared with intravenous nitroglycerin or placebo amongst patients with acutely decompensated HF.¹⁸ As a result, nesiritide was used as baseline therapy in the treatment of patients with acute decompensated HF. However, in the ASCEND-HF (Acute

Table 1. Impact of the management of acute heart failure on medium-term and long-term prognosis.

Study	Year	Patients	Intervention	Results
VMAC ¹⁸	2002	489	Nesiritide (142) vs nitroglycerin (143) vs placebo (142)	Nesiritide was superior to nitroglycerin and placebo in reducing pulmonary capillary wedge pressure; the study did not focus on death or rehospitalizations
OPTIME ²⁰	2002	951	Milrinone (479) vs placebo (472)	Milrinone was not superior to placebo in reducing death or rehospitalizations in the short and medium term and was associated with a higher risk of arterial hypotension and arrhythmias
VERITAS ²⁵	2007	1435	Tesozentan (730) vs placebo (718)	No changes were observed <i>versus</i> placebo
SURVIVE ²²	2007	1327	Levosimendan (664) vs dobutamine (663)	Levosimendan was not superior to dobutamine in reducing mortality at 180 days after an event of decompensated heart failure
REVIVE 2 ²³	2013	700	Levosimendan (350) vs placebo (350)	Levosimendan was not superior to placebo in improving short-term and medium-term prognosis
EVEREST ²⁶	2007	4133	Tolvaptan (2072) vs placebo (2061)	Tolvaptan was not superior to placebo in improving short-term and medium-term prognosis
ASCEND HF ¹⁹	2011	7007	Nesiritide (3496) vs placebo (3511)	There were no differences in reducing death or rehospitalizations for heart failure
PROTECT ²⁷	2011	2033	Rolofylline vs placebo	No benefits of rolofylline were observed on renal function, without data about medium-term and long-term evolution
RELAX-AHF 2 ²⁴	2019	6545	Serelaxin (3274) vs placebo (3271)	No effects of serelaxin on mortality or worsening of heart failure at 180 days of follow-up

Table created with data from refs.^{18,19,20,22–27}

Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial, nesiritide had no impact on the rate of death and rehospitalization, with a small effect on dyspnoea and a higher risk of hypotension.¹⁹ After this study, nesiritide was not recommended for routine use in patients with acute HF.

With regard to inotropes, the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) trial showed that intravenous milrinone, a phosphodiesterase 3 inhibitor that increases heart contractility and decreases pulmonary vascular resistance, did not reduce the median number of days of hospitalization for cardiovascular causes, in-hospital mortality, or the composite incidence of death or readmission.²⁰ Furthermore, it increased the risk of hypotension requiring intervention and new atrial arrhythmias, not supporting its use in the treatment of patients hospitalized for an exacerbation of chronic HF.²⁰

With respect to inodilators, levosimendan, a calcium sensitizer with positive inotropic effects and vasodilatory effects, showed encouraging results in initial studies. In the LIDO (Levosimendan Infusion versus Dobutamine)

study, levosimendan was superior to dobutamine in improving haemodynamics in patients with low-output HF.²¹ The SURVIVE (Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support) trial aimed to assess the effects of a short-term intravenous infusion of levosimendan or dobutamine on long-term survival in patients hospitalized with acute decompensated HF who required inotropic support. In this study, although a higher reduction in natriuretic peptides was observed with levosimendan, all-cause mortality at 180 days was similar between both groups.²² In the REVIVE (Randomized Evaluation of Intravenous Levosimendan Efficacy) trial, although levosimendan provided rapid and durable symptomatic relief, its use was associated with an increased risk of adverse cardiovascular events.²³

Serelaxin is a recombinant form of human relaxin 2, a hormone that increases blood output of the heart and blood flow in the kidney and has vasodilator properties. Although previous studies had suggested symptom relief after serelaxin use in patients with acutely decompensated HF, the RELAX-AHF-2 (second Relaxin in Acute Heart Failure) trial did not show a beneficial effect of

serelaxin on the incidence of death from cardiovascular causes at 180 days or worsening HF at 5 days compared with placebo.²⁴ In summary, none of these drugs has had a positive impact on the risk of medium-term or long-term survival or HF hospitalization amongst patients with acutely decompensated HF (Table 1).

More recently, venoarterial extracorporeal membrane oxygenation (ECMO) has shown good results in patients with cardiogenic shock. A retrospective study of patients with cardiogenic shock treated with venoarterial ECMO exhibited survival rates at 3 months, 12 months and 2 years of 72%, 65% and 57%, respectively.²⁸ However, the use of ECMO is not recommended in patients with acutely decompensated HF but without low-cardiac output. Therefore, there are important limitations in the current management of acute HF. As a result, a comprehensive approach to the management of these patients in all phases of the disease – from HF worsening to the outpatient setting – is warranted.

Definition of vulnerable period in HF

Each acute HF event has a relevant effect on heart structure and function. Additionally, in-hospital treatment has a marginal impact on the long-term course of HF. Consequently, after hospitalization for HF, the patient is at particular risk of new readmission or death.¹¹ The vulnerable period has been defined as the time between HF decompensation up to 6 months after discharge.⁶ Although this definition is currently in use, some aspects are worth further consideration. Because of the generation of the original definition, we propose a redefinition of the vulnerable period, considering five components:

1. **It is a phase of the natural history of HF.** The HF course has different phases that range from an asymptomatic period, despite cardiac structural damage, to a period of stability of symptoms, interrupted with acute decompensations. Early identification of each phase is mandatory to define specific diagnostic and therapeutic actions.
2. **It is characterized by acutely worsening HF, with or without a previous history of HF.** The main characteristic of patients in the vulnerable period of HF is that they all present with an event of worsening HF, either progressive deterioration in patients with a history of chronic HF or abruptly in previously asymptomatic patients. Regardless, the exacerbation of HF represents the progression of the disease, the loss of efficacy of compensatory mechanisms, the participation of potentially preventable events (acute coronary syndromes, arrhythmias, infections) or therapeutic failure (inadequate management, lack of adherence or persistence to the

recommendations performed by the health professionals).

3. **It requires priority medical attention at the in-hospital and outpatient level.** Because acute HF is a serious clinical entity, the treatment of patients must be prompt, comprehensive and far-reaching. Of note, although most patients with an episode of acute HF will require in-hospital management, there is a significant proportion of individuals who are not hospitalized despite having data that show worsening symptoms. The foregoing responds to various situations such as the different hospital infrastructure available in various countries and the saturation of health services as well as new assistance programmes, including HF outpatient clinics or day hospitals, that offer decongestive therapy with intravenous diuretics for those who present with signs of non-severe acute decompensation. In addition, there are patients who attend the emergency department because of worsening symptoms and who receive intravenous therapies but who are not hospitalized. Of note, this latter scenario has been included as part of the primary endpoint of some contemporary clinical trials.²⁹
4. **Duration of vulnerability during worsening HF.** The duration for considering the vulnerable period of HF has changed in recent years and has moved from weeks to months. In fact, data from observational studies have shown that the risk of major cardiovascular events persists up to 6 months after the exacerbation episode;⁶ consequently, close monitoring of patients should be prolonged up to 6 months after the worsening of symptoms.
5. **Patients in this period are at increased risk of major cardiovascular events.** It has been estimated that the risk of rehospitalization or death can reach up to 30% and 10% of patients, respectively, during the first weeks after an episode of HF worsening,¹¹ which is significantly higher than observed after an acute coronary syndrome.

As a result, we propose redefining the vulnerable period, as follows: 'a phase of the natural history of HF that is characterized by an episode of acute worsening in patients with or without a previous history of HF, which requires priority medical attention at the in-hospital and outpatient level and that can be prolonged up to 6 months after worsening of symptoms. Its main property is that patients in this period are at increased risk of major cardiovascular events'.

According to this consensus, we have divided the vulnerable period into three time periods: early, intermediate and late (Table 2). This classification allows the definition of specific actions that can be taken for the treatment of patients in each of the phases of the vulnerable period.

Table 2. Classification of vulnerable period in patients with acute HF.

Period	Definition
Early period	From the beginning of the symptoms of decompensation, including hospitalization or outpatient urgent medical attention, to the first month after the acute event
Intermediate period	From 1 to 3 months after the worsening HF episode
Late period	From 3 to 6 months after the worsening HF episode

HF, heart failure.

Management strategies during the vulnerable period of HF

Although the vulnerable period of HF represents the greatest risk of death and readmissions, it should also be considered as the best window of opportunity to start or optimize HF treatment. In this sense, in each of the phases of the vulnerable period, there are specific actions that will help the health team, patients and their relatives to improve the clinical course of the disease, reducing the risk of major cardiovascular events and improving prognosis. From a practical point of view, we present a proposal of interventions for each of the stages of the vulnerable period.

Early vulnerable period

This period represents the most critical moment for patients and therefore requires specific actions to overcome the exacerbation of HF, prepare hospitalized patients for discharge, make the transition from intravenous to oral treatment, initiate non-pharmacological treatment and cardiac rehabilitation, implement pharmacological treatment for the chronic phase of HF, and educate patients, family members and caregivers about the main aspects of HF management. The proposed actions during this phase of the vulnerable period are described below.

Recognition and management of acute HF

Early recognition of the signs of acute HF is essential. The delay in diagnosis favours the worsening of the clinical course of HF.³⁰ Therefore, it is important that patients receive education about the recognition of alarm signs such as worsening of dyspnoea or fluid retention.³¹ Additionally, considering that not all hospitals or clinics have cardiologists in the emergency department, it is necessary to implement continuing medical education actions for the recognition of acute HF for non-cardiologists.

In the same way, it is necessary to have complementary tests that allow increased precision of the diagnosis in an acute scenario. Based on available evidence, natriuretic peptides stand out for their important position in ruling out HF;^{32,33} chest X-ray also provides supportive added value for the diagnosis; and, more recently, pulmonary ultrasound allows the identification of cases of congestion in patients with acute dyspnoea.³⁴ Ideally, tertiary hospitals should have non-invasive cardiovascular imaging support, particularly echocardiography, for the patient assessment.^{2,17} Additionally, other biochemical markers, such as troponins, urea, serum electrolytes and transaminases, have shown their utility in the stratification of patients and the identification of multiorgan involvement in acute HF.¹⁷

Once the diagnosis is made, it is essential to immediately implement therapeutic measures recommended by clinical practice guidelines according to each patient's haemodynamic clinical profile. The specific treatment of acute HF is outside the objectives of this article and is explained extensively in current clinical practice guidelines and consensus documents.^{2,17,35}

Evaluation of patients before discharge

One of the most important challenges for the clinician is to define the improvement of patients after receiving treatment for acute HF. Particularly in the field of congestion, it has been documented that approximately 40% of cases persist with sub-clinical pulmonary congestion data at hospital discharge.³⁶ This is important because, as mentioned previously, the main haemodynamic profile of patients with acute HF is congestion without low-cardiac output and the persistence of congestion is one of the most important predictors of acute HF recurrence.³⁷ Because of clinical improvement can be subjective, the addition of diagnostic tools, such as measuring natriuretic peptide levels and conducting lung and inferior vena cava ultrasound, facilitates the identification of those patients who show improvement in their clinical-haemodynamic condition after being treated. In the first case, it is suggested that a decrease of $\geq 30\%$ from the initial value of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is capable of predicting a lower risk of readmission for HF at 200 days of follow-up,³⁸ so the addition of this tool in hospital care protocols is convenient and should be considered as a standard of care.

Similarly, lung ultrasound has become a useful tool with a close correlation with natriuretic peptide levels. Its implementation as an additional tool in the diagnosis and clinical evaluation of patients with acute HF should be encouraged because of its usefulness, low cost and the fact that it poses no risk to patients.³⁹ Figure 1 shows a decongestion evaluation proposal and Table 3 shows

a comprehensive evaluation of volume status at discharge.⁴⁰ Additionally, it is important that patients show stable renal function before hospital discharge.^{2,35}

Therapeutic optimization during hospitalization

Because of in-hospital management of acute HF has a marginal impact on the long-term prognosis of the disease, it is essential that all patients start or restart treatment that has been considered to modify disease progression. Regarding pharmacological management, changing from intravenous diuretics to oral diuretics is important once the clinical and haemodynamic improvement of patients has been established. An effective diuretic regimen is definitive to achieve decongestion in patients with acute HF.³⁵ Figure 2 presents a proposal for diuretic adjustment during this phase. Likewise, the inhibition of neuroendocrine overexpression using angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and mineralocorticoid receptor antagonists (MRAs) is essential and should be considered for all patients with HFrEF.^{2,17} It is recommended that patients with new-onset acute HF who are naive to these treatments start them before hospital discharge once stability is achieved. On the other hand, patients with an episode of acute decompensation of chronic HF must maintain disease-modifying treatment during hospitalization, if their clinical-haemodynamic condition allows, and undergo adjustment before discharge, with the purpose of favouring its use in all cases of HFrEF.

Recently, angiotensin II and neprilysin antagonists (ARNIs) have been shown to be superior to ACE inhibitors in reducing major cardiovascular events in patients with chronic

HFrEF;⁴¹ in the field of acute HF, the PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial⁴² demonstrated that in-hospital administration of sacubitril–valsartan was superior to enalapril in reducing blood levels of NT-proBNP (–46.7% vs –25.3%; HR 0.71, 95% CI 0.63–0.81; $p < 0.001$), which represents a greater capacity of ARNIs to reduce the haemodynamic overload of the insufficient heart. Moreover, this reduction was evident as early as week 1. In addition, no greater worsening of renal function, hyperkalaemia, symptomatic hypotension and angio-oedema were reported with sacubitril–valsartan than for enalapril. However, it remains unknown whether this change translates into fewer outcomes in the months following hospitalization for HF. Therefore, at this moment, both classes of drugs are acceptable in this clinical context. Regarding sodium–glucose co-transporter 2 (SGLT2) inhibitors, the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)²⁹ and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction)⁴³ studies consolidated the role of these drugs as an essential part of the treatment of patients with chronic HFrEF.^{2,17} In this sense, the SOLOIST-WHF study⁴⁴ demonstrated that, in a group of patients with diabetes and a recent episode of acute HF, sotagliflozin administered during the pre-discharge phase or in the first month after discharge, was superior to placebo in reducing cardiovascular death and HF readmissions as well as visits to the emergency department (HR 0.67, 95% CI 0.52–0.85; $p < 0.001$). Similarly, the EMPULSE study⁴⁵ showed that the administration of empagliflozin 10 mg OD in patients hospitalized

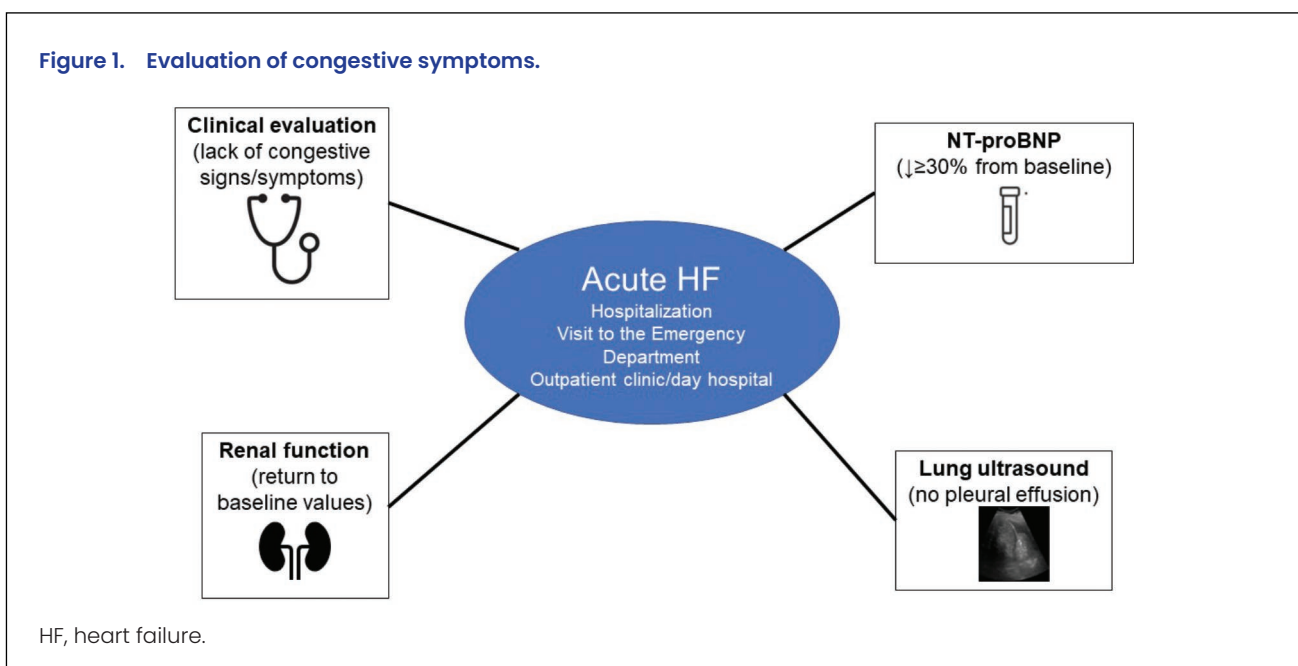


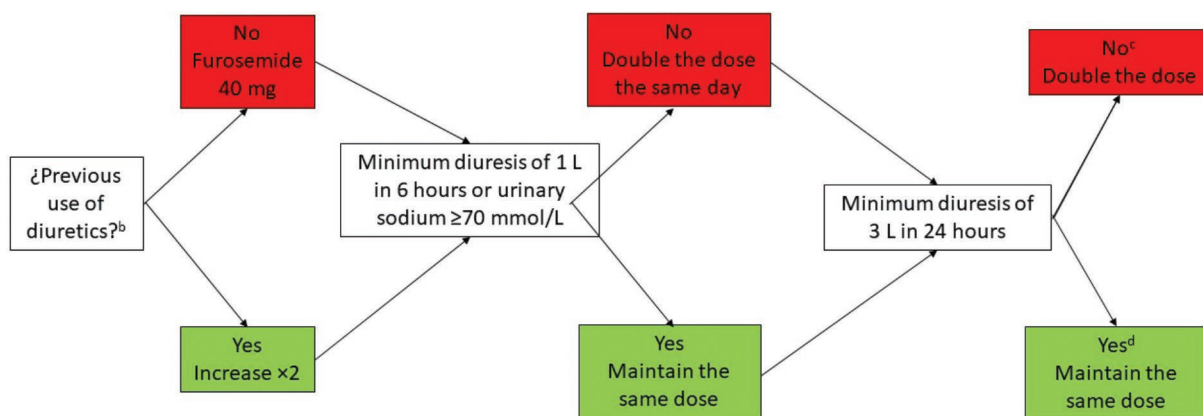
Table 3. Comprehensive evaluation of volume status at discharge.

Variable	Congestion				
	Euvolaemia	Mild	Moderate	Severe	
Clinical evaluation	Orthopnea	No	Mild	Moderate	Severe
	Elevated jugular venous pressure/hepatojugular reflux	No	I	II	III
	Oedema	No	+	++	+++ /++++
	6-Minute walk test (meters)	300–400	200–300	100–200	<100
Complementary tests	NT-proBNP (pg/mL)	<400	400–1500	1500–3000	>3000
	Ca 125 (U/mL)	<35	>35	>35	>35
	Chest X-ray	Normal	Pulmonary venous congestion	Pulmonary venous congestion + pleural effusion	Interstitial oedema
	Vena cava imaging	<22 mm with collapsibility >50%	>22 mm or collapsibility <50%	>22 mm or collapsibility <50%	>22 mm with collapsibility <50%
	Lung ultrasound	>15 B-lines	15–30 B-lines	15–30 B-lines	>30 B-lines

NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Table modified from ref.⁴⁰

Figure 2. Diuretic adjustment during acute HF episode.^a



^aThe use of loop diuretics should be limited to the control of congestion.

^bIf the patient is already taking mineralocorticoid receptor antagonists (MRAs) and no marked deterioration of renal function or hyperkalaemia is observed, maintain MRA treatment.

^cConsider the introduction of MRAs in case of naive patients (or uptitration of MRA dosage if already taking) to increase diuresis.

^dConsider the introduction of MRAs in case of naive patients when reduction of loop diuretics dose starts, in patients without marked deterioration of renal function or hyperkalaemia.

for acute HF, who were close to hospital discharge, resulted in significant differences compared with placebo for the composite primary endpoint, defined as clinical benefit that included death from any cause, number of HF episodes, time to first HF event, and an improvement of 5 points or more in the global score of the Kansas City Cardiomyopathy quality of life questionnaire at 90 days (stratified win ratio 1.36, 95% CI 1.09–1.68; $p=0.0054$).

More recently, in the DICTATE-AHF trial that included 240 patients hospitalized for acute HF, requiring intravenous loop diuretics, patients received dapagliflozin 10 mg once daily or structured usual care until day 5 or hospital discharge. Dapagliflozin significantly increased 24-hour natriuresis and 24-hour urine output and significantly decreased time to completing intravenous diuretic therapy and time to hospital discharge, without increasing the risk of side-effects.⁴⁶ In this sense, we recommend that all hospitalized patients with acute HF and who are stable receive quadruple therapy (ARNIs/ACEIs plus beta-blockers plus aldosterone inhibitors plus SGLT2 inhibitors) regardless of whether they are treatment naive or are already receiving these drugs. Because of the efficacy and safety of these drugs, it is recommended that they are prescribed as soon as possible, either before discharge or, at a maximum, within 4 weeks after hospital discharge. This is important because, if therapy is not started at hospital or within a few days after discharge, it is very likely that appropriate guideline-recommended therapy will not be completely instituted, leading to an increased risk of death and rehospitalization for HF within the first several weeks.¹³

This must be accompanied by the appropriate control of symptoms and other comorbidities, such as iron deficiency, diabetes, renal failure and atrial fibrillation, amongst others. Iron deficiency in HF is a common, sometimes underestimated, comorbidity found in almost half of the population with chronic HF.²⁵ The determination of serum ferritin and percentage of transferrin saturation should be used routinely in the diagnosis and follow-up of HF as recommended by current guidelines (recommendation I, level of evidence C).²⁵ Clinical trials have demonstrated the benefits of IV iron carboxymaltose;^{47–49} the AFFIRM-AHF trial reported that, in patients with iron deficiency and ejection fraction (EF) of <50% who were stabilized after an episode of acute HF, treatment with ferric carboxymaltose was safe and reduced the risk of new HF hospitalizations, with no apparent effect on the risk of cardiovascular death.⁵⁰ Therefore, IV iron carboxymaltose should be considered the treatment of choice in these patients to improve symptoms and functional class and is also recommended by current guidelines (recommendation IIa, level of evidence A).^{2,5}

Therefore, it is important to recognize the presence of these clinical conditions in all patients with HF to provide a comprehensive therapeutic approach (Table 4).³⁵ Table 5 shows practical guidance for the start and up-titration of disease-modifying HF drugs during the early vulnerable phase.

It is important to make the health team responsible for patient care so that these recommendations can be implemented because real-world evidence indicates that no more than 56% of patients who are discharged after an episode of acute HF receive a disease-modifying drug therapy, which may translate to an increased risk of death and rehospitalization for HF.⁵¹

To achieve this goal, safety barriers can be implemented, such as checklists that verify the appropriate pharmacological prescription before hospital discharge. Initiatives, such as the Optimize Heart Failure Care programme, have shown that these simple instruments can make a great difference in favour of the appropriate prescription of pharmacological treatments during the vulnerable period.⁵² Figure 3 shows an example of a checklist in pre-discharge and during early follow-up of patients with HF.

Education of patients, relatives, and caregivers and non-pharmacological therapies

HF is a chronic condition and much of the success relies on adherence to or persistence with treatment. Therefore, the empowerment of patients, their families and caregivers is of great importance. For this, it is impor-

Table 4. Management of common comorbidities in patients with heart failure.

Iron deficiency	Consider ferric carboxymaltose if: <ul style="list-style-type: none"> • Ferritin <100 µg/L or • Ferritin 100–300 µg/L and transferrin saturation <20%
Diabetes	<ul style="list-style-type: none"> • Target HbA1c <7.0% • SGLT2i + other antidiabetics to attain HbA1c • Avoid thiazolidinediones, sulfonylureas, saxagliptin
Atrial fibrillation	<ul style="list-style-type: none"> • Anticoagulation (preferably DOACs vs VKA) • Preferably rhythm control vs heart rate control (consider ablation)

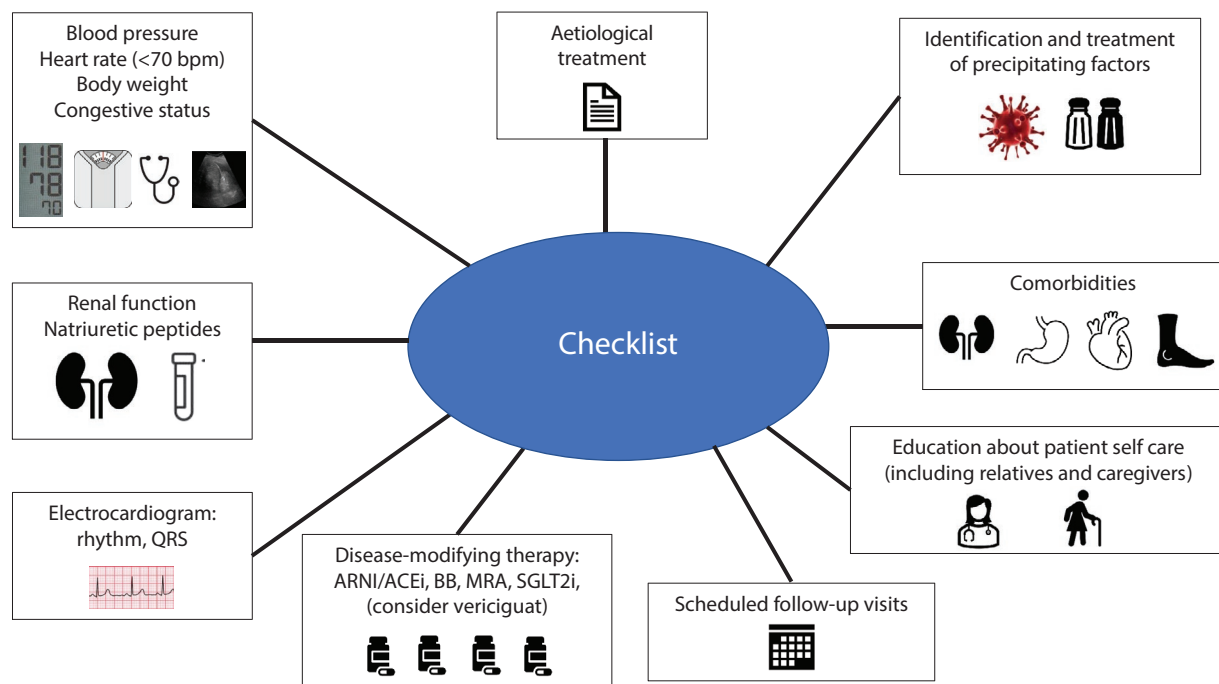
DOACs, direct oral anticoagulants; HbA1c, glycated haemoglobin; SGLT2i, sodium–glucose cotransporter 2 inhibitors; VKA, vitamin K antagonists.

Table 5. Practical guidance for the start and uptitration of disease-modifying heart failure drugs during the early vulnerable phase.

Drug	Pre-discharge	Visit 1 (7–14 days)	Visit 2 (21–28 days)	Follow-up visits
Sacubitril–valsartan	Start at low doses	Same dose	Uptitrate if tolerated	Uptitrate if tolerated
ACE inhibitors	Start at low doses	Same dose	Uptitrate if tolerated	Uptitrate if tolerated
Bisoprolol/carvedilol	Start at low doses	Uptitrate if tolerated	Uptitrate if tolerated	Uptitrate if tolerated
Spironolactone/eplerenone	Start at low doses	Same dose	Uptitrate if tolerated	Same dose
Dapagliflozin/empagliflozin	Start	Same dose	Same dose	Same dose
Ivabradine	–	Start at low doses (patients at sinus rhythm, HR >75 bpm despite beta-blocker use)	Uptitrate if tolerated	Same dose
Vericiguat ^a	–	Consider starting at low doses in symptomatic patients (NYHA II–IV)	Uptitrate if tolerated	Same dose

ACE, angiotensin-converting enzyme; HR, heart rate. ^aVericiguat is not available in Mexico at this moment.

Figure 3. Checklist in pre-discharge and early follow-up of patients with HF.



ACEi, angiotensin-converting enzyme inhibitors; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

tant that, before being discharged, patients and their families receive an educational intervention about the early recognition of alarm signs, the importance of self-monitoring (vital signs, daily weight, symptoms, questionnaires), nutrition, sodium and fluid intake, physical activity, and proper medication management. Members of the health team, such as the HF nurse, should participate in this process. From this perspective, it is desirable that, whenever possible, patients can be incorporated into structured HF programmes.¹⁷

Follow-up visits

After an acute HF episode, all patients should be reassessed early, either after hospital discharge or after visiting the emergency department. Loss of follow-up of patients is a common cause of treatment abandonment and increases the risk of major cardiovascular events. In addition, inadequate follow-up precludes patients from optimizing pharmacological treatment, either regarding the type of drugs or doses required. Moreover, in patients who are not re-evaluated early, it is not possible to identify likely adverse events related to treatment. Consequently, it is recommended that patients should be followed-up within a period of no more than 2 weeks from hospital discharge or emergency room visit through the implementation of a structured follow-up, considering all healthcare professionals, particularly nurses and physicians. Importantly, this should be adapted to local particularities to achieve maximum success.

At the follow-up visit, the following actions should be taken:

1. Clinical evaluation, determination of vital signs, physical examination, assessment of data suggestive of pulmonary or systemic congestion, and evaluation of functional class.
2. Pharmacological treatment adjustments: initiate drugs that were not prescribed at hospital discharge and/or dose titration (ARNIs/ACEIs, beta-blockers, MRAs, SGLT2 inhibitors), dose adjustment of loop diuretics.
3. Identification of potential adverse events related to drugs.
4. Identification of patients that should receive complementary therapies, such as intravenous iron, or candidates for devices (i.e. implantable cardioverter defibrillator or cardiac resynchronization therapy).
5. Reinforcement of education for patients, relatives and caregivers.
6. Complementary diagnostic procedures, that is, tests that could not be performed during the acute phase of the disease.

In this sense, the use of patient diaries for symptoms and vital signs, whether in printed or electronic formats, have

proven to be extraordinarily useful tools to reinforce patient empowerment and obtain a more objective understanding of a patient's clinical evolution. In addition, patient diaries facilitate communication between members of the health team and allow continuity of treatment; therefore, their systematic use is highly recommended.

Intermediate vulnerable period

It is important to continue the monitoring of all patients during this phase of the vulnerable period. The main goal is to achieve the early optimization of treatment. The frequency of these visits must be individualized for each patient. However, it is recommended that the time between visits does not exceed 4 weeks. During these visits, the following items should be assessed and implemented:

1. Evaluate the persistence of congestion from a clinical, biochemical and radiological point of view.
2. Review of complementary tests: natriuretic peptides, serum electrolytes, urea, haemogram and iron parameters.
3. Dose adjustment or withdrawal of loop diuretics: although it is uncommon that patients with HF do not require loop diuretics, it is recommended that, in those cases where there is no evidence of congestion (clinical, biochemical or radiological), they receive the minimum dose of loop diuretics or even withdrawal.
4. Optimization of disease-modifying therapy and dose titration of ARNIs/ACEIs, beta-blockers, MRAs and SGLT2 inhibitors.¹⁷ For this, it is recommended that structured dose-titration protocols are followed to quickly and safely reach the maximum tolerated dose in the shortest possible time. Supplementary Figures 1 and 2 (available at: <https://www.drugsincontext.com/wp-content/uploads/2023/12/dic.2023-8-1-Suppl.pdf>) show a proposal for dose titration of renin-angiotensin system antagonists and beta-blockers in patients with HF rEF.
5. Drugs for specific situations. Recent guidelines^{2,53} consider vericiguat as an alternative for therapeutic optimization in patients with a history of recent hospitalization for HF. This recommendation is based on the results of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial.⁵⁴ Vericiguat is an oral guanylate cyclase stimulator that favours the formation of cyclic guanosine monophosphate, improving the formation of nitric oxide and leading to a reduction of oxidative stress, a condition that is common in patients with HF. In the VICTORIA study,⁵⁴ patients with HF rEF received either vericiguat or placebo added to standard therapy to compare the effects of this drug on a composite primary endpoint of cardiovascular death or hospitalization for HF. This study is of special interest

for two reasons that deserve to be highlighted to ensure its correct interpretation and application in clinical practice. The first aspect relates to the selection criteria where, in addition to including patients with HF with left ventricular EF of <45% and high levels of natriuretic peptides, all patients were required to have a recent history of a worsening episode of chronic HF. In other words, the study was developed specifically in patients during the vulnerable period of the disease. Thus, the population was divided into three groups based on the time elapsed because of the worsening of symptoms. The first group consisted of patients with a hospitalization for HF within 3 months prior to randomization, the second included patients who were hospitalized for acute HF within 3–6 months prior to randomization, and the third included patients who had received intravenous diuretics in the 3 months prior to randomization even without requiring hospitalization. The second important aspect to highlight is that most of patients included in the VICTORIA study were receiving optimized treatment for chronic HF, with 60% of patients receiving triple neurohormonal control therapy (ACEIs/ARNIs, beta-blockers, MRAs), of which 15% received ARNIs. Additionally, 32% had a device (implantable cardioverter defibrillator, cardiac resynchronization therapy), which distinguishes the VICTORIA trial from contemporary clinical trials. The results of the VICTORIA trial showed that, compared with placebo, the addition of vericiguat to standard treatment significantly reduced the primary composite of cardiovascular death and/or hospitalization for HF (HR 0.90, 95% CI 0.82–0.98; $p=0.02$). In addition, a lower risk of the composite of death from any cause or hospitalization for HF was observed (HR 0.90, 95% CI 0.83–0.98; $p=0.02$) as well as HF hospitalization (HR 0.90, 95% CI 0.81–1.00). However, no significant reduction in cardiovascular death risk was shown with vericiguat (HR 0.93, 95% CI 0.81–1.06) (Table 6). With regard to safety concerns, although a higher proportion of cases of mild hypotension were observed in patients who received vericiguat, this fact did not have a negative impact on drug withdrawal or the worsening of HF or renal function. The evidence points to a new tool that may be useful to improve the clinical course of HF in patients receiving standard treatment who are in the vulnerable period of HF. Therefore, from our perspective, the early use of vericiguat must be considered in this clinical scenario.

Resting heart rate control is a variable that has been systematically underreported in the management of HF despite solid evidence of the benefits that adequate control has on the clinical course of the disease. The SHIFT (Systolic Heart failure treatment with the IF inhibitor ivabradine Trial) study⁵⁵ demonstrated that, in a cohort of patients with chronic HFrEF, in sinus rhythm, and with a heart rate of ≥ 70

bpm despite beta-blockers, the addition of ivabradine to standard treatment reduced the risk of HF hospitalizations and cardiovascular death by 18% (HR 0.82, 95% CI 0.75–0.90; $p<0.0001$), admissions for worsening HF by 26% (HR 0.74, 95% CI 0.66–0.83; $p<0.0001$) and deaths because of HF by 26% (HR 0.74, 95% CI 0.58–0.94; $p=0.014$). As a result, ivabradine is recommended by clinical practice guidelines as an adjuvant therapy to beta-blockers for heart rate control.^{2,17,53} Regarding the vulnerable period, a post-hoc analysis of the SHIFT study⁵⁶ showed that patients with chronic exposure to ivabradine had a lower risk of rehospitalization for HF after recent HF hospitalization. Additionally, there is evidence suggesting that the combination of ivabradine with beta-blockers is useful to achieve the titration of beta-blockers, a relevant situation in the field of therapeutic optimization from the perspective of maximum tolerated doses (Table 5).⁵⁷

According to clinical evidence, 58–83% of patients during an episode of acute decompensated HF may have iron deficiency even in the absence of anaemia, in contrast to 35–55% of patients with chronic HF.⁵⁸ Iron deficiency, defined as a ferritin concentration of <100 $\mu\text{g/L}$ or 100–300 $\mu\text{g/L}$ and transferrin saturation of <20%, has become a prognostic marker in HF and, at the same time, a therapeutic target.^{2,17,58} Iron deficiency negatively impacts on functional capacity, quality of life, hospitalizations and mortality. Fortunately, treatment with ferric carboxymaltose improves quality of life and reduces hospitalizations in this population.^{59,60} Therefore, we recommend that iron kinetics should be evaluated to define candidates that need to receive intravenous iron supplementation.

6. Enhance education for patients, families and caregivers. At every follow-up visit, the educational message on self-care, health promotion and medication management should be reinforced as should the recognition of alarm signs. Additionally, the maintenance of open communication channels between patients and the health team should be reinforced beyond visits to the emergency room in order to recognize possible episodes of worsening HF early and act immediately, thus avoiding the progression of damage. These channels can be implemented in different ways and by optimizing the tools of information and communication technologies, which may include telephone calls, video calls, chats, social networks, emails or software specifically designed for monitoring.
7. Assess therapeutic adherence. Along with education, evaluation of therapeutic adherence is essential. This can be achieved through simple techniques such as interview, drug count or patient records. The HF nurse has a relevant role to play regarding this point and should always promote the need for adherence and persistence to treatment.

Table 6. Clinical characteristics and main results of contemporary clinical trials of patients with HFREF.

	PARADIGM HF (n=8399) sacubitril/ valsartan	DAPA-HF (n=4744) dapagliflozin	EMPEROR- Reduced (n=3730) empagliflozin	VICTORIA (n=5050) vericiguat
Inclusion criteria				
NT-proBNP cut-off, pg/ml	≥600 or ≥400 if HFH <12 months	≥600 or ≥400 if HFH <12 months (SR); ≥900, regardless history of HFH (AF)	Varied with EF	≥1000 (SR) ≥1600 (AF)
eGFR cut-off, mL/min/1.73 m ²	≥30	≥30	≥20	≥15
LVEF cut-off, %	≤35	≤40	≤40	<45
Recent HF decompensation	Not required	Not required	Chronic HF ≥3 months	HFH <6 months or IV diuretic use <3 months
Baseline data				
NYHA class III or IV	25%	32%	25%	41%
Median NT-proBNP, pg/mL	1608	1437	1906	2816
HFH <3 months ago	19%	8%	31% (HFH ≤12 months)	67%
HFH <6 months ago	31%	16%		84%
Efficacy data				
Primary outcome	First HFH or CV death	Worsening HF ^a or CV death	First HFH or CV death	First HFH or CV death
Median follow-up, months	27	18	16	11
Primary endpoint, events per 100 patient-years (control arm)	13.2	15.6	21.0	37.8
Primary endpoint, HR (95% CI) ARR	0.80 (0.73–0.87) 2.7	0.74 (0.65–0.85) 4.0	0.75 (0.65–0.86) 5.2	0.90 (0.82–0.98) 4.2
CV death, HR (95% CI) ARR	0.80 (0.71–0.89) 1.5	0.82 (0.69–0.98) 1.4	0.92 (0.75–1.12) 0.6	0.93 (0.81–1.06) 1.0
First HFH, HR (95% CI) ARR	0.79 (0.71–0.89) 1.6	0.70 (0.59–0.83) 2.9	0.69 (0.59–0.81) 4.8	0.90 (0.81–1.00) 3.2

AF, atrial fibrillation; ARR, absolute rate reduction; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalization; HFREF, heart failure with reduced ejection fraction; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SR, sinus rhythm.

^aUnplanned hospitalization/urgent visit resulting in IV therapy for HF.

Table created with data from refs.^{29,41,43,54}.

8. Identification of possible adverse drug reactions. Pharmacovigilance systems should be strengthened, especially in those countries in which this practice is poorly developed. This will allow a better understanding of the balance between the risk-to-benefit ratio of polypharmacy to which patients are exposed and is particularly useful in the redesign of care processes.

A special mention is made regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs). The risk of hospitalization for HF whilst on NSAIDs was studied by

Page and Henry,⁶¹ with NSAID users found to have a relative risk (RR) of 2.1 when compared with non-users. In patients with established cardiovascular disease, the RR was noticeably higher (10.5). According to the authors, NSAID use might play a role in up to 19% of cases of newly diagnosed congestive HF. Mamdani et al.⁶² compared the risk of hospitalization for HF in patients treated with coxibs, non-selective NSAIDs and controls. The most significant risk was found in patients on rofecoxib (RR 1.8, 95% CI 1.5–2.2). The RR in users of non-selective NSAIDs was 1.4 (95% CI 1.0–1.9). Celecoxib was not associated with an

increased risk. Heerdink et al.⁶³ showed an RR of hospitalization for HF of 1.8 (95% CI 1.4–2.4) when NSAIDs were administered to patients treated with diuretics. The authors did not find a significant difference between individual NSAIDs, which suggested a class effect. The highest risk of HF decompensation was present within the first days of treatment initiation and gradually decreased to the level of placebo after 1 month. In conclusion, adequate monitoring for signs of adverse effects with proper patient education are required to increase patient safety during NSAID therapy. The duration of NSAID treatment should be limited as much as the clinical situation allows and only the minimal effective dose should be used.⁶⁴

Late vulnerable period

During the late phase of the vulnerable period, it is relevant not to reduce patient care because it is common that, once clinical stability has been reached, health professionals and patients reduce supervision and monitoring of the disease. It is critically important that, during this phase, in which many patients are referred to primary care physicians or non-cardiologist specialists, patients receive optimal pharmacological and non-pharmacological treatment.

During this period, follow-up visits should include:

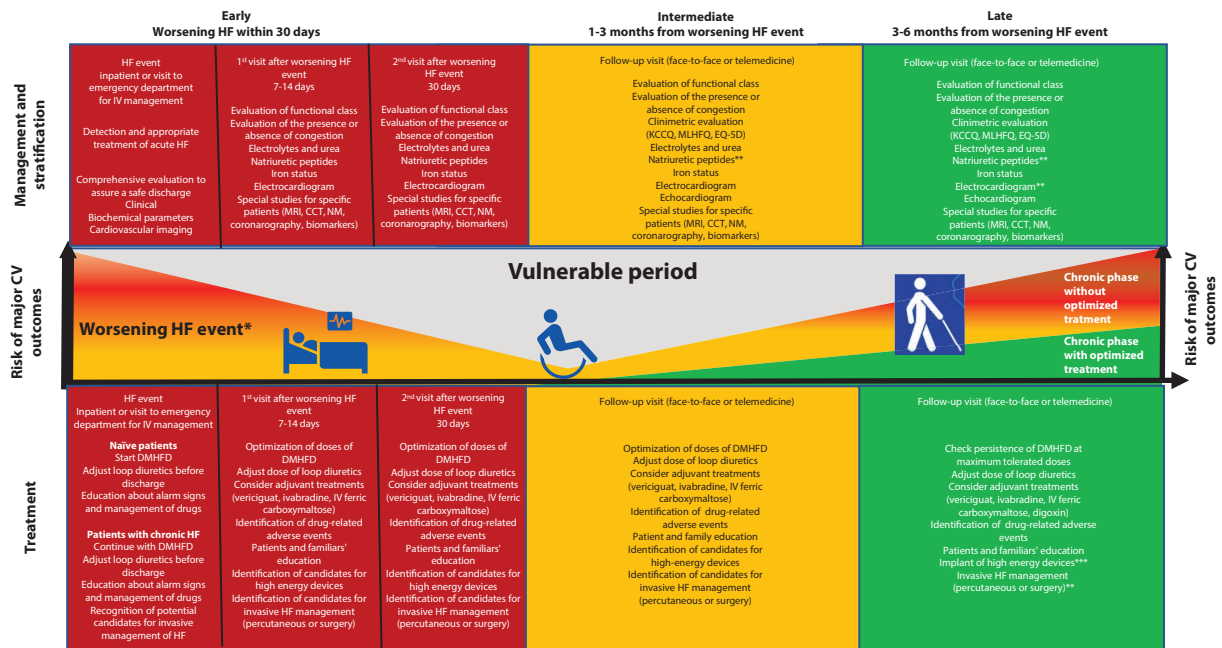
1. Clinical evaluation. In addition to the determination of vital signs, physical examination and functional class, it is recommended that the functional capacity of patients is determined objectively through interventions such as a 6-minute walk test. Likewise, questionnaires such as the Kansas City Cardiomyopathy tool are especially useful for evaluating the impact of symptoms on the quality of life of patients. This evaluation, together with the interpretation of the complementary diagnostic tests, will allow each patient to be stratified and for appropriate follow-up management to be defined, with referral either to the primary care setting, advanced HF unit (i.e. need for heart mechanical assistance or heart transplantation), or palliative care programmes, according to each case.
2. Complementary tests. It is desirable to maintain monitoring using biochemical markers (natriuretic peptides, urea, serum electrolytes, hepatic transaminases) as well as non-invasive cardiovascular imaging studies, particularly echocardiography and, if appropriate, cardiac magnetic resonance. The results of these studies can be compared with those of the acute phase once therapeutic optimization has been achieved, defining the next steps to follow.
3. Maintain optimized pharmacological treatment. Ensure that all patients have reached optimal medical treatment at the maximum tolerated doses. This is very relevant, because real-life studies have shown that a significant proportion of patients do not receive

optimal pharmacological treatment in terms of type of drugs or dose reached. Of note, this phenomenon is aggravated in those patients who have had a recent HF hospitalization.⁶⁵

4. Identification of those patients suitable for implantable cardioverter defibrillator or cardiac resynchronization therapy. Cardiac resynchronization therapy is considered a disease-modifying treatment as the proportion of responders in well-selected patients is reasonably high. In responders, not only do symptoms improve but it also prevents the progression of myocardial damage and reduces mortality; therefore, it is important that no more than 3 months elapse before identifying patients who are potential candidates for cardiac resynchronization therapy.^{2,17} Similarly, implantable cardioverter defibrillators are indicated as secondary prevention of sudden cardiac death and as primary prevention in patients with HFrEF of ischaemic origin, with evidence of severe myocardial damage (left ventricular EF <35%) and who have received optimized medical treatment for at least 3 months. In patients with HFrEF of non-ischaemic origin, the current recommendation is class IIa, derived from the benefits offered by optimal pharmacological therapy on this outcome (ARNIs, beta-blockers, MRAs, SGLT2 inhibitors). Therefore, it must be ensured that patients are treated optimally before defining the need for the device.
5. Assess disease progression and identify patients with advanced HF. Despite optimized treatment, some patients may progress to advanced stages. It is important to recognize this condition to consider the appropriate therapeutic measures, including invasive management of HF, particularly in those patients who are potential candidates to be evaluated in transplant programmes or requiring long-term mechanical circulatory support.
6. Define the patient journey and comprehensive follow-up. Because it is impossible for all patients to be followed-up in only a single level of care, it is important to integrate the different healthcare levels to ensure the continuity of the therapeutic process. Therefore, comprehensive care protocols are useful for defining the best time for patient referral, always maintaining communication between all members of the health team.

Figure 4 summarizes the strategies for assessment and HF management during the vulnerable period. The strategies for the management of patients with HF during the vulnerable period are multiple and require training and specific professional skills as well as the systematization of care processes to ensure that all measures can be implemented adequately. Therefore, it is desirable to promote the creation and development of HF programmes and clinics to integrate all actions in the best way and

Figure 4. Comprehensive strategy for evaluation and management of patients with heart failure during the vulnerable period.



*with or without hospitalization, ** according to physicians' judgment, ***in patients with previous optimization of HF drugs

CCT, cardiac computed tomography; CV, cardiovascular; DMHFD, disease-modifying HF drugs; EQ-5D, EuroQoL-5D; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living-With-Heart-Failure Questionnaire; MRI, magnetic resonance imaging; NM, nuclear medicine.

in the shortest possible time. These programmes, with a multidisciplinary approach, have been shown to improve the clinical outcomes of patients and are also attractive from a pharmacoeconomic point of view.⁶⁶⁻⁶⁸ Within these, physicians and nurses with specific training on HF should be considered as the cornerstone of the HF team, with a particular role in coordination, communication, education and patient monitoring. In addition, other healthcare professionals (for example, nutritionists, psychologists, electrophysiologists, interventional cardiologists, cardiac surgeons, pneumologists and nephrologists) can also participate in the management of these patients according to their specific requirements.

Conclusions

The vulnerable period of HF represents a real crisis in the natural history of the disease, as it is associated

with a marked risk of readmission or death. Like any crisis, it maintains a duality that expresses risk and opportunity. The early optimization of treatment is mandatory during the vulnerable period to reduce the risk of adverse events. Importantly, from this document, it is concluded that, from an opportunistic point of view, the vulnerable period constitutes the best moment for therapeutic optimization of HF, making rational use of all available therapies with the sole purpose of improving the quality of life and prognosis of patients. For this purpose, we divided the management strategies into three periods (early, intermediate and late vulnerable period), including not only pharmacological options but also evaluation and education, with the complete implication of the cardiology team, which mainly includes physicians, nurses and other specialists implicated in the management of HF.

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