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First Mexican statement in Heart Failure

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Sacubitrilo/Valsartan: La inhibición de la Neprilisina en ICrEF

5 años después de PARADIGM-HF

El efecto de Sacubitrilo/Valsartan versus Enalapril en el entorno clínico, mecanistico y desenlaces en calidad de vida en pacientes con ICrEF*

	Efecto estimado* (95% ci)
Muerte Cardiovascular o Hospitalización por insuficiencia cardiaca	0.80 (0.73, 0.87) 20%↓
Muerte Cardiovascular	0.80 (0.71, 0.89) 20%↓
Hospitalización por Insuficiencia cardiaca	0.79 (0.71, 0.89) 21%↓
Todas las causas de muerte	0.84 (0.76, 0.93) 16%↓
Primera y/o recurrente hospitalización por Insuficiencia cardiaca	0.77 (0.67, 0.89) 23%↓
Visita a urgencias por Insuficiencia cardiaca	0.66 (0.52, 0.85) 24%↓

Un consistente beneficio de sacubitrilo/valsartan tanto en muerte cardiovascular como en hospitalizaciones por insuficiencia cardiaca fue observado en todos los subgrupos de pacientes con insuficiencia cardiaca con fracción de eyección reducida examinados en PARADIGM HF

Edad	<75yr	0.78 (0.71, 0.86)
	≥75yr	0.86 (0.72, 1.04)
Fracción de eyección	≤35%	0.78 (0.72, 0.86)
	>35%	0.89 (0.68, 1.16)
Tasa de filtración glomerular	<60ml/min/1.73m²	0.79 (0.69, 0.90)
	≥60ml/min/1.73m²	0.80 (0.71, 0.90)
Presión arterial sistólica	≤120mmHg(median)#	0.79 (0.71, 0.89)
	>120mmHg(median)#	0.81 (0.71, 0.92)
NT-pro BNP	≤1,615pg/ml(median)†	0.73 (0.63, 0.84)
	>1,615pg/ml(median)†	0.83 (0.75, 0.93)

↑ Aumento de la calidad de vida
↑ Mejoría en la clase funcional NYHA

↓ NT-pro BNP
↑ GMP c
↓ Troponina
↓ Señalización Pro-fibrotica
↓ sST2

↓ Volumen ventrículo izquierdo
↓ Volumen aurícula izquierda
↓ Relación E/e´ valvula Mitral

↓ Deterioro de la filtración glomerular

↓ Presión arterial sistólica

*ICrEF: Insuficiencia cardiaca con fracción de eyección reducida

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First Mexican statement in Heart Failure

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Introduction
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Introducción
Primer Posicionamiento Nacional en Insuficiencia Cardiaca

José Antonio Magaña Serrano,[1] José Ángel Cigarroa López,[1] Adolfo Chávez Mendoza,[1] Jorge Rayo Chávez,[1] Héctor Galván Oseguera,[1] Luisa Fernanda Aguilera Mora,[2] Juan Betuel Ivey Miranda,[1] Rafael Rascón Sabido,[3] Gustavo Francisco Mendez Machado,[4] Genaro Hiram Mendoza Zavala,[5] Luis Olmos Dominguez,[1] Sergio Chávez Leal,[6] Marcos Jaciel Olalde Román,[1] María de Jesús Fernández Muñoz,[7] Moisés Aceves García,[1] Ernesto Pombo Bartelt,[8] Alex Daniel Pacheco Bouthillier,[2] Gerardo de León Larios,[9] Hugo Enrique Coutiño,[10] Vitelio Augusto Mariona Montero,[11] Jorge González,[12] Edgar Hernández Rendón,[1] Amada Álvarez San Gabriel,[13] Rolando Joel Álvarez Álvarez,[13] Carlos Alberto Guízar Sánchez,[13] Diego Araiza Garaygordobil,[13] Eduardo Heberto Herrera Garza,[14] David Castán Flores,[15] Vicente Eduardo Ruiz Ruiz,[16] Antonio Tepayotl Aponte,[1] Pedro Gutiérrez Fajardo,[17] Gabriela Borrayo Sánchez,[17] Marco Antonio Alcocer Gamba[18]

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Heart Failure has become the main concern in cardiovascular medicine in developed and emergent countries and Mexico is no exception. As such, it constitutes the common denominator of all the diseases that affect the cardiovascular system and therefore, the magnitude of the problem is enormous.

In recent decades, great advances have been made in the diagnosis and treatment of heart failure, which have been reflected in the recommendations of current clinical practice guidelines. However, despite having excellent consensus documents, the magnitude of the problem and its impact on morbidity and mortality continue to increase.

For this reason, it is necessary to have tools that help clinicians to put into practice the recommendations of the guidelines through a critical and individual analysis of the situation in each country, its human resources, the installed infrastructure, and the needs and areas of opportunity. To improve patient care.

From the above, the idea arises of generating the first national statement on heart failure, a document that will accompany the clinical practice guidelines.

The objective is to have a consensus of national experts to generate awareness of the unmet needs in the early detection and timely treatment of heart failure in all its manifestations and specific scenarios, through a patient-centered approach and with a vision of multidisciplinary and comprehensive approach.

For this, an experienced work team was formed that, through the analysis of the most relevant and current scientific evidence, as well as the experience of the most representative work groups and centers of excellence on heart failure in Mexico, contributed a critical and proactive vision of the problem in question.

Through 10 chapters, the authors propose the implementation of the best clinical practices for the diagnostic approach, comprehensive treatment, emerging special situations, the

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creation of heart failure centers and programs, and the need to increase the participation of Mexico in research and projects at a global level which by now, are redirecting the destinies of this disease.

We are grateful for the academic endorsement of the National Association of Cardiologists of Mexico and the Mexican Society of Cardiology, who with the support of this effort contribute to improving the cardiovascular health of the Mexican population.

We hope that this document will be useful for all the health personnel who today treat patients with heart failure and that it will be a national reference to improve the care of this vulnerable group.

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First Mexican statement in Heart Failure

Primera declaración Mexicana en materia de Insuficiencia Cardiaca

José Antonio Magaña Serrano,[1] José Ángel Cigarroa López,[1] Adolfo Chávez Mendoza,[1] Jorge Rayo Chávez,[1] Héctor Galván Oseguera,[1] Luisa Fernanda Aguilera Mora,[2] Juan Betuel Ivey Miranda,[1] Rafael Rascón Sabido,[3] Gustavo Francisco Mendez Machado,[4] Genaro Hiram Mendoza Zavala,[5] Luis Olmos Dominguez,[1] Sergio Chávez Leal,[6] Marcos Jaciel Olalde Román,[1] María de Jesús Fernández Muñoz,[7] Moisés Aceves García,[1] Ernesto Pombo Bartelt,[8] Alex Daniel Pacheco Bouthillier,[2] Gerardo de León Larios,[9] Hugo Enrique Coutiño,[10] Vitelio Augusto Mariona Montero,[11] Jorge González,[12] Edgar Hernández Rendón,[1] Amada Álvarez San Gabriel,[13] Rolando Joel Álvarez Álvarez,[13] Carlos Alberto Guízar Sánchez,[13] Diego Araiza Garaygordobil,[13] Eduardo Heberto Herrera Garza,[14] David Castán Flores,[15] Vicente Eduardo Ruiz Ruiz,[16] Antonio Tepayotl Aponte,[1] Pedro Gutiérrez Fajardo,[17] Gabriela Borrayo Sánchez,[17] Marco Antonio Alcocer Gamba[18]

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I. EPIDEMIOLOGY, DEFINITION, ETIOLOGY AND CLASSIFICATION

In the United States and European Union countries, the prevalence of heart failure (HF) is close to 2% of the total adult population.[1,2] With an incidence of more than 600 thousand new cases per year only in the United States. In addition, HF is the leading cause of hospitalization in people older than 65 years, with a poor prognosis and overall survival of 50% at five years after the diagnosis. In Mexico, there is a lack of a reliable National Registry to allow a precise knowledge of the size of this public health problem. This is relevant since cardiovascular diseases are the leading cause of death and disability in our country.[3] Moreover, the prevalence of high blood pressure, diabetes and obesity in Mexico is one of the highest in the world and it is well known that these conditions are HF precursors. ***It is therefore, urgent and essential to have a Heart Failure National Registry*** that allows us to know the number and characteristics of the affected population to design health policies aimed to prevent the disease and diminish the harm for those who suffer from it.

According to this positioning, heart failure (HF) should be conceptualized as a: «***Clinical syndrome resulting from any functional or structural alteration that affects the heart's ability to fill or contract*».**

According to this definition, 3 components stand out:

1. The first is to point out HF as ***a syndrome*** and not as a specific nosological entity. The significance of this is to consider that HF represents the common denominator of all diseases that directly or indirectly affect the cardiovascular system since each of them has the ability to develop HF as part of its natural history.
2. Secondly, it should be noted that the ***involvement*** can be ***structural and/or functional*** and a patient is not required to have severe alterations in the cardiac structure to consider him as a HF patient.
3. Finally, it is important to emphasize the ***importance of the diastolic*** function and not just the contractile capacity of the heart. This component represents one of the essential requirements for the

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diagnosis of HF with Preserved Ejection Fraction (HF-pEF).

As a syndrome, HF is a multicausal entity. By now, the most common etiology is ischemic heart disease; however, virtually all conditions affecting the cardiovascular system are causes of HF, highlighting high blood pressure, heart valve diseases, cardiomyopathies, and congenital heart diseases, among others. In developing countries, conditions such as rheumatic heart disease and Chagas cardiomyopathy remain a major cause of HF. In addition, there are non-cardiac conditions that in their natural history, or by direct cardiotoxic effects, are considered causes of HF, for example, Diabetes Mellitus, dysthyroidism and, relevantly, cardiotoxicity associated to chemotherapy agents used to treat cancer *(Table 1)* describes HF causes and highlights most common causes in Mexico.

Once a HF patient is identified, it is important to classify him comprehensively. To do this, various parameters should be considered to allow the physician to identify relevant aspects that guide the integration of a complete and individualized therapeutic scheme.

Therefore, it is proposed to classify every HF patient based on the following criteria:

1. Clinical stage.
2. Functional class (NYHA).
3. Ejection fraction (LVEF).
4. Etiology.

Table 2 summarizes the characteristics of each HF classification criteria.

An applied example in daily practice would be:

«56-year-old male, with history of two myocardial infarctions, medium-effort dyspnea and echocardiogram with LVEF of 35%».

Corresponding to a ***Heart Failure patient with Reduced Ejection Fraction (HF-rEF), ACC/AHA stage C, NYHA Functional Class II, and ischemic aetiology.*** Treatment should consider

Table 1: Heart failure causes.

Cardiac	Extracardiac	Iatrogenic
Ischemic heart disease	Diabetes mellitus	Drugs (i.e. chemotherapy-induced cardiotoxicity)
Systemic arterial hypertension	Dysthyroidism	Surgical or invasive procedures complications
Valvular heart disease:	Chronic Obstructive Pulmonary Disease	Radiotherapy
• Congenital	Renal failure (cardiorenal syndrome)	
• Degenerative	Anemia	
• Inflammatory (rheumatic)	Thoracic trauma	
• Infectious (endocarditis)	Secondary cardiac tumors (metastases)	
Cardiomyopathies:	Immunologic	
• Dilated	Infectious (e.g. Chagas and HIV)	
• Restrictive	Peripartum cardiomyopathy	
• Hypertrophic	Alcoholic cardiomyopathy	
Myocarditis	Deposit cardiomyopathies (e.g. amyloidosis)	
Congenital heart diseases	Pulmonary arterial hypertension	
Rhythm and conduction disturbances		
Pericardial disease		
Primary cardiac tumors (Ej. Mixoma)		
Pulmonary embolism		

* Ischemic heart disease, high blood pressure, diabetes, and heart valve disease are common causes of heart failure in Mexico.

Table 2: Heart failure integral classification.

Type of classification			
Clinical stage (ACC/AHA)	Functional class (NYHA)	Left ventricular ejection fraction (LVEF)	Ethiology
A Risk factors or heart failure causing diseases (HBP, DM, Obesity) Without cardiac structural alteration No symptoms of heart failure	I Asymptomatic patients or with dyspnea on great exertion only	Reduced ejection fraction (HF-rEF) LVEF < 40%	Ischemic
B Alterations of the cardiac structure No past or present symptoms of heart failure	II Medium efforts dyspnea	Moderately Reduced Ejection Fraction (HF.mREF) LVEF 41-49%	Non-ischemic (the cause of heart failure must be specified)
C Alterations of the cardiac structure Present and/or past signs and symptoms of heart failure	III Dyspnea on small efforts, patient comfortable at rest	Preserved ejection fraction (HF-pEF) LVEF > 50% No LV dilation Diastolic dysfunction Elevation of natriuretic peptides	
D Stage C characteristics plus advanced or treatment refractory heart failure data, recurrent heart failure hospitalizations	IV Rest dyspnea Orthopnea Paroxysmal nocturnal dyspnea		

ACC/AHA = Joint Working Group of the American College of Cardiology and the American Heart Association, NYHA = New York Heart Association, LVEF = Left ventricular ejection fraction, HBP = High Blood Pressure, DM = diabetes mellitus, HF-rEF = Heart Failure with Reduced Ejection Fraction, C-Fer = Heart failure with reduced ejection fraction, HF-mREF = Heart Failure with moderate Reduced Ejection Fraction, HF-pEF = Heart failure with preserved ejection fraction, LV = left ventricle.
* The criteria described are not mutually exclusive, are complementary and necessary to achieve a comprehensive classification of patients with heart failure.

not only the management of the ischemic heart disease, but all measures of proven use for symptomatic patients with HF-rEF.

II. DIAGNOSTIC APPROACH AND STRATIFICATION

Heart failure diagnosis should be early, accurate and comprehensive.

Therefore, it is necessary to generate a clinical suspicion in a timely manner to contain the damage progression to advanced stages of the syndrome. It is proposed that this suspicion should be made based on the clinical data and medical history.

While HF is a broad syndrome with multiple signs and symptoms *(Table 3)*,[4] it highlights the presence of ***three pivotal data*** found in most patients:

1. Effort dyspnea, resting dyspnea or paroxysmal nocturnal dyspnea,

2. Low tolerance to physical activity, and
3. Evidence of hydrosaline retention due pulmonary congestion and/or peripheral oedema.

Therefore, an intentional search of this data and other signs should be performed on any patient with suspected HF and must be extremely accurate in the semiology of each positive data.

Regarding medical history, all history of diseases with direct involvement of the cardiovascular system such as ischemic heart disease or high blood pressure, as well as non-cardiac situations that can potentially affect the structure and heart function, such as exposure to cardiotoxic agents or metabolic diseases such as diabetes and dysthyroidism, should be considered.

It is worth mentioning that there are special cases in which de novo HF may develop without prior diseases, such as acute myocarditis in previously healthy patients. Clinical picture usually involves serious signs and symptoms that guide the diagnosis. For this reason, despite the absence of a suggestive background, the diagnosis should not be ruled out.

It is ***important that all medical personnel regardless of their specialty should be able to generate the diagnostic suspicion of HF.*** This, in order to be able to identify as many patients as possible from early disease stages.

Once there is a suspicion of HF, it should be confirmed through diagnostic aids. Among the most important are: electrocardiogram, biochemical markers, non-invasive cardiovascular imaging and invasive hemodynamics.

Table 3: Heart failure signs and symptoms.

Symptoms	
Common	**Rare**
• Dyspnea • Orthopnea • Paroxysmal nocturnal dyspnea • Low functional capacity and easy fatigue	• Night cough • Loss of appetite • Confusion • Depression • Palpitations • Vertigo or dizziness • Syncope • Bendopnea
Signs	
Specific	**Unspecific**
• Jugular plethora or hepatojugular reflux • Third heart sound (ventricular gallop) • Apical impulse displaced down and to the left (as a substitute for cardiomegaly)	• Weigh gain (>2 kg/week) • Weight loss (in advanced HF) • Cachexia • Peripheral edema • Pulmonary rales • Tachycardia • Irregular pulse • Tachypnea • Hepatomegaly • Ascites • Cold limbs • Oliguria • Decreased amplitude of peripheral pulses

Modified from: Ponikowski P et al.[4]

1. Electrocardiography (EKG)

It is essential that every patient with suspicion or diagnosis of HF has electrocardiographic studies. Since 9 out of 10 patients with chronic HF show some abnormalities in EKG and 98% of acute patients show electrocardiographic alterations.[5]

While there are no pathognomonic data from HF, there are relevant data that guide the clinician for the decision-making. Within the data that are mandatory to take into consideration we find:

a. **Identification of the rhythm.** It is desirable that patients with HF are kept at a sinus rhytm because this ensures the atrial contribution to cardiac output. Recognition of rhythm disturbances is essential for therapeutic adjustments, for example atrial fibrillation in patients with HF is a leading criteria for oral anticoagulation.[6]
b. **Left or right ventricle enlargement.** EKG is useful for demonstrating this type of structural alteration and greatly supports early detection of high-risk patients, such as patients with high blood pressure and left ventricular hypertrophy in whom cardiac structural damage is already identified, and

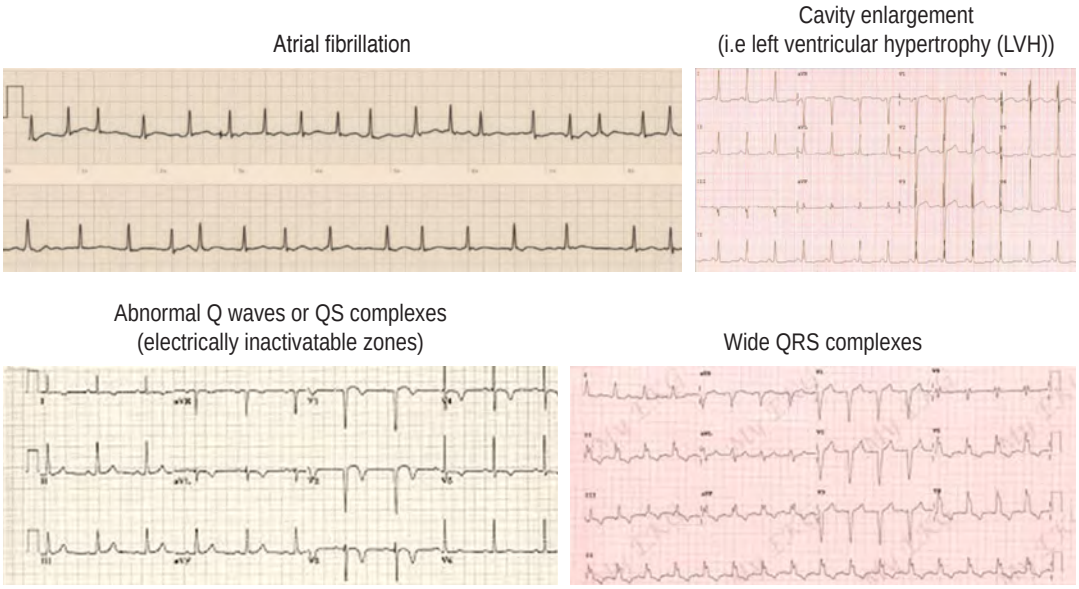


Figure 1: Heart failure frequent electrocardiographic findings. QRS.

guides the doctor for the use of disease-modifying treatments. There are also cases of hypertrophic cardiomyopathy where the electrocardiogram is particularly useful for strengthening diagnostic suspicion that will be confirmed through imaging.

c. **Presence of pathological Q waves or electrically inactivated areas.** This finding is common in patients with a history of myocardial infarction but may be found in other situations where myocardial tissue has been replaced by fibrosis, such as patients with cardiac amyloidosis or other forms of infiltrative heart disease.
d. **QRS complex duration.** This is of particular interest because it is one of the most robust criteria for interventricular dyssynchrony. Thus, a QRS greater than 130 msec places the patient with HF in the field for decision-making for modern therapies indication, such as cardiac resynchronization, moreover, if it is accompanied by left branch blocking images.

In addition, in patients with syncope, lipothymias or perception of palpitations, continuous electrocardiographic monitoring (Holter) and in special cases, the use of electrophysiological studies is recommended. *Figure 1*, summarizes the most relevant electrocardiographic findings in HF.

2. Biochemical markers, hematology, and clinical laboratory

There is a large diversity of analytes that are used as biochemical markers for the diagnosis, monitoring and prognosis of patients with HF. Therefore, its rational use and interpretation are fundamental in the approach of patients. The main biomarkers in HF are:

a. **Natriuretic peptides.** In situations of increased hemodynamic stress, atrial and ventricular cardiomyocytes synthesize natriuretic peptides which function is to promote diuresis and vasodilation, in order to try to reduce the hemodynamic overload of a heart in failure. Additionally, these peptides offer cardioprotective benefits because they have antiproliferative, antifibrotic, anti-apoptotic propierties and they are modulators of renin angiotensin aldosterone system. From a clinical point of view, the most studied is the B type Natriuretic Peptide (BNP). An elevation of serum BNP levels or pro-peptide aminoterminal fraction (NT-proBNP) indicates significant hemodynamic overload. The main usefulness of determining these peptides lies in their ability to exclude HF, so that in patients with acute dyspnea and

normal levels of natriopeptides, the diagnosis of HF can be excluded by more than 90%. This is especially important in emergency rooms where a large number of patients attend with dyspnea as a reason for consultation, as it allows to discern between cardiac and non-cardiac causes of dyspnea and based on it, take therapeutic decisions immediately. For this reason, ***it is recommended to have the BNP or NT-proBNP*** test available at any hospital with emergency department as part of diagnostic tools for the study of patients with acute dyspnea. *Table 4* shows the cut-off points of natriuretic peptides to exclude a diagnosis of HF.[4,7,8]

Other usefulness of these biochemical markers lies in their power to define patient prognosis, particularly during the vulnerable phase of the disease. Hence, a patient hospitalized for acute HF who shows clinical improvement, after receiving treatment and their levels of natriuretic peptides decrease by 30% or more from baseline, has a lower risk of rehospitalizations due to acute HF, while that patient with clinical improvement but no decrease in the concentration of these substances or even an elevation, will have an increased risk of relapses so, his hospital discharge and treatment for the chronic phase of the disease must be reconsidered *(Figure 2)*.[9] Therefore, ***it is suggested that whenever possible, levels of natriuretic peptides should be measured before***

Table 4: Cut points to exclude heart failure based on natriuretic peptides blood levels.

Situation	Clinical scenario	BNP (pg/mL)	NT-proBNP (pg/mL)	Comments
Patients with heart failure suspicion	Non-acute patients	< 35	< 125	• When the value of natriuretic peptides is below these levels, the diagnosis of Heart Failure is unlikely
	Acute patients	< 100	< 300	• It is necessary to consider other diagnoses

BNP = B-type natriuretic peptide, NT-proBNP = Aminoterminal fraction of pro-natriuretic peptide type B.
Ponikowski P et al.[4]

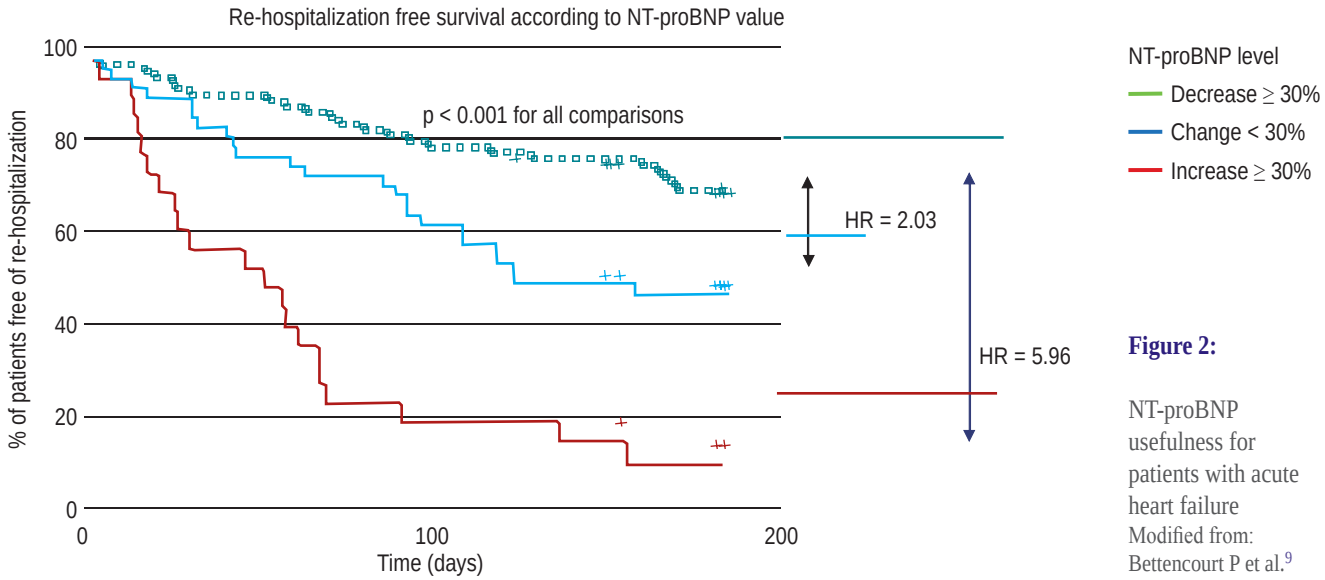


Figure 2:

NT-proBNP usefulness for patients with acute heart failure
Modified from: Bettencourt P et al.[9]

egressing patients, after an episode of acute heart failure.

It should be noted that there are important aspects to consider for the proper use of natriuretic peptides. Among the most relevant we find the pre-analytical variability and the use of specific drug treatments. With regard to the first point it should be noted that BNP has a short plasma half-life (about 20 minutes) while NT-proBNP as an inactive molecule, has greater stability with a plasma half-life of about 120 minutes, this aspect is relevant due to the possibility of having erroneous results if the processing of the sample suffers dilation, so to avoid this it is recommended, whenever possible, to use *«Point of Care»* (POC) systems that are able to make the determination in minutes and at the head of patients.[10] On the other hand, in patients under treatment with neprylisin antagonists, a BNP determination is not useful so it is recommended to use NT-proBNP[8] in these cases.

b. **Troponins.** They are markers of myocardial damage. While their main usefulness has been in the field of acute coronary syndromes, in HF it has been shown that small elevations in high sensitivity troponin T or I concentration, have an important prognostic value.[11] So contemporary clinical practice guidelines recommend them as additional elements in the comprehensive diagnostic approach of the patient with HF.[4] In our midst, at this time, its employment cannot be generalized as a mandatory indication; however, if the resource and feasibility are available for determination, ***it is desirable that the determination of high-sensitivity troponins be incorporated into the biochemical profile of patients under comprenhesive Heart Failure study.***

c. **Kidney function.** Multiorganic injury in HF is common in both the chronic and acute phases of the disease. In this sense, renal dysfunction is a condition of particular relevance since patients with HF and kidney damage, a Cardiorenal Syndrome, have a worse prognosis than those with preserved renal function. According to the European Registry of HF, the discrete elevation of serum creatinine levels (1.3 mg/dL) has proven to be a 1-year mortality predictor (HR 1.75, 95% CI 1.75-2.10).[12] Similarly, in RELAX-2 study, patients with acute HF a serum creatinine increase of 0.3 mg/dL during 48h of hospital admission, demonstrated a significant increase in mortality at 180 days of hospitalization (1.76, 95% CI 1.11-2.82, p = 0.016);[13] also, an increase in the Cystatin C value of ≥ 0.3 mg/dL doubled the risk of cardiovascular death in the medium term (HR 2.1 95% CI 1.38-3.20, p - 0004).[13] Similarly, the systematized use of markers of renal function is important as part of patient follow-up and therapeutic response, in HF natural history, the impaired renal function defines the prognosis of patients and on the other hand, there are useful drugs for heart failure management which if used improperly may have damaging effects on renal function. Therefore, ***it is essential to consider the evaluation of renal function in the diagnostic approach and monitoring of HF patients***.

d. **Sodium and potassium.** Serum sodium levels are of great relevance to the prognosis of HF. Hyponatremia (Serum Na^+ less than 130 mEq/L) has shown to increase the risk of death at 1 year with a risk increase of 48%.[12] On the other hand, the unnapropied use of diuretics, particularly those with a natriuretic effect, is often associated with volume and sodium depletion. Elevated serum potassium is common in patients with renal dysfunction, as well as in patients under management with mineralocortidoid receptor antagonists. Serum potassium levels above 5.5 mEq/L increase the risk of developing cardiac arrhythmias. Therefore, ***it is essential that every HF patient has sodium and potassium blood levels as part of their diagnostic approach and monitoring.***

e. **Complete blood count and iron kinetics.**[14] According to clinical trials and real-world studies, the frequency of anemia in HF ranges from 10 to 55%. Similarly, Iron deficiency ranges from 35 to 55% in chronic patients and reaches 80% in the acute phase. The consequences of this cover ultrastructural and clinical aspects that have prognostic value in HF (see comorbidities and special situations). For this reason, ***the diagnostic approach of HF needs to consider a complete blood count and iron kinetics.***

f. **Glycemia and glycosylated hemoglobin.** Diabetes increases the risk of developing

HF and diabetic or dysglycemic patients with HF have a worse prognosis than normoglycemic patients. For this reason, the early recognition of diabetic patients is necessary, regardless of the HF type (HF-rEF, HF-pEF or HF-mREF).[15] ***It is therefore essential to have fasting blood glucose quantifications and, when possible, glycosylated hemoglobin (HbA1c) determinations for every HF patient and diabetes.***

g. **Liver function.** Like a renal failure, liver failure is a common alteration in advanced stages of HF and occurs frequently in cases of severe acute HF. In patients with acute HF, a 20% increase in transaminases levels (ALT or AST) versus baseline, increases between 66 and 96% of the risk of cardiovascular death at 6 months of internment.[13] In chronic patients, hepatic congestion by systemic venous hypertension conditions the compression of bile duct resulting in increased alkaline phosphatase and if this condition persists then could develop centrolobulillary necrosis and irreversible liver damage. Accordingly, ***it is recommended that patients with acute HF and those with Stage C and D heart failure have transaminase and alkaline***

Table 5: Heart failure chemical biomarkers.

Biomarker	Usefulness		Comments
	HF diagnosis	Comprehensive evaluation and prognosis of HF	
Natriuretic peptides (BNP, NT-proBNP)	x	x	The BNP or NT-pro BNP test should be available in every hospital establishment with emergency services Whenever possible, levels of natriuretic peptides should be quantified before discharging patients hospitalized for acute HF
High sensitivity tro-ponins		x	It is desirable to incorporate the measurement of high sensitivity troponins into the biochemical profile of a patient under heart failure assessment
Serum electrolytes		x	It is essential that all patients with heart failure have blood levels of sodium and potassium as part of their diagnostic approach and monitoring
Renal functions tests		x	It is essential to consider the assessment of the renal function during the diagnostic process and monitoring patients with HF
Liver function tests		x	It is recommended that patients with acute HF and those with HF in advanced stages have an assessment of transaminases, alkaline phosphatase and, if possible, complete liver function tests
Blood count, iron kinetics		x	A complete blood count and iron kinetics must be considered in the diagnostic approach to heart failure
Fasting blood glucose, glycosylated hemoglobin		x	It is essential that all patients with heart failure have fasting blood glucose quantification and, whenever possible, the determination of glycosylated hemoglobin (HbA1c) is performed as a control criterion during the follow-up of patients with HF and Diabetes
Special tests (genetics, microbiology, molecular biology)	x	x	All structured programs for heart failure management need access to the performance of special tests for the complete diagnosis of selected patients

HF = heart failure, BNP = B type Natriuretic Peptide, NT-proBNP = Amino Terminal Pro type B Natriuretic Peptide.

phosphatase assessments and if possible complete liver function tests.

h. **Special studies.** Special genetic mapping studies should be considered in situations such as cardiomyopathies with suspected genetic origin (i.e. Family dilated cardiomyopathy). In infiltrative cardiomyopathies such as amyloidosis it is necessary to perform tests such as the differentiation between primary amyloidosis, and those due to transthyretine deposits. Similarly, in cases with suspected Chagas disease, serological diagnosis testing is mandatory. Therefore, ***it is necessary that all structured programs for HF management have access to special tests such as those already described.***

Table 5 summarizes the indications and usefulness of biochemical markers in HF.

3. Noninvasive cardiovascular imaging

Imaging studies are a critical tool for the diagnostic approach of HF. There are currently several modalities. The most relevant are:

a. **Echocardiogram.**[4] This is the most accessible cardiovascular imaging study, it allows to know relevant structural parameters and the cardiac function in real time or even on the patient's bedside.

This is the first-choice study for the estimation of the left ventricular ejection fraction (LVEF), although it presents an insufficient parameter for estimating the systolic function, it is essential to know the type of HF. For the calculation of this parameter, the use the modified Simpson method is recommended.

However, beyond LVEF, an echocardiogram is useful for determining the overall and regional ventricular function, diastolic function, valve and subvalvular anatomy and functionality, congenital malformations, estimation of various hemodynamic parameters such as pressure gradients, and cardiac synchrony and dyssynchrony.[16,17]

Recently, the new Strain techniques, Speckle tracking and three-dimensional echocardiogram, have been added to the echocardiographic protocols and provide relevant information in specific cases.[16,17]

In addition, special modalities such as transesophageal echocardiography and stress echocardiogram are useful for identifying structures and images not accessible with the transthoracic approach or for the identification of ischemia, myocardial viability and contractile reserve in patients with chronic ischemic heart disease, low flow and low gradient aortic stenosis, as well as in dynamic mitral insufficiency, so they are recommended in certain clinical scenarios.[17]

In the practice of cardio oncology, the echocardiogram has provided relevant data to identify early cardiotoxicity-related data from the use of cancer management drugs, making it possible to take preventive and containment measures in a timely manner. Therefore, ***an echocardiogram should be mandatory for any HF patient*** regardless of the type of HF as part of the diagnostic approach and chronic monitoring. Special modalities will be at medical discretion depending on each specific scenario.

Figure 3 summarizes the applications and usefulness of echocardiography in heart failure.

b. **Radiological studies and chest tomography.**[4] Conventional radiology remains the gateway to the noninvasive imaging studies. Both, chest x-ray in posteroanterior projection and cardiac series, provide images that are useful for defining the cardiac structure as well as a lung pathology, particularly lung congestion in acute cases. Its main advantage is the easy access and low cost however, professional competences are necessary for the proper interpretation of radiological findings including recognition of the limitations of the images obtained. It is recommended ***that every patient with HF have a basic chest radiological study.***

Regarding a chest tomography in HF, its routine use is not recommended, however, this study may be useful for HF with intermediate probability of coronary artery disease, so in certain cases and based on the treating physician's opinion, it could be used as an adjuvant to a comprehensive study protocol.[18]

On the other hand, in HF patients with suspected or confirmed SARS-CoV-2 virus infection, chest tomography takes on full

importance to identify the degree of lung engagement and has important value for the therapeutic decision-making and prognosis of these patients,[19] hence ***the use of a chest tomography is recommended for every patient with HF and suspicion or confirmation of SARS-CoV-2 virus infection.***

c. **Magnetic resonance imaging (MRI).** Magnetic resonance imaging is an non-invasive imaging modality that has been successful in various medical specialties. In Cardiology, its applications are diverse and include the possibility to evaluate:

c.1. **Characterization and detection of fibrosis.**[20-23] By using special agents and sequences, such as late Gadolinium reinforcement (LGS), it is possible to obtain images that clarify the etiology of specific clinical conditions such as Fabry disease, sarcoidosis, myocarditis, cardiac amyloidosis and Chagas disease, among others. The accuracy of a Cardiac MRI has been compared to that of an endomyocardial biopsy but with less risk. For this reason, it is particularly useful in the study of cardiomyopathies of unidentified origin. It is important, as a safety measure to note that in patients with eGFR < 30 mL/min/1.73m^2 BS, Gadolinium should not be used due to the risk of promoting acute renal damage.[24]

c.2. **Cardiac dyssynchrony.**[25] Along with the new echocardiographic modalities, Cardiac MRI is useful for the study of cardiac synchrony and dyssynchrony; however, to date this study should not be considered as a major selection criterion for deciding cardiac resynchronization therapy.

c.3. **Right ventricular function.**[26,27] It is the gold standard for the study of right cavities so it should be considered as the preferred option in patients with HF and significant Right Ventricle involving.

c.4. **Diastolic function.**[27] In special cases of patients with heart failure with preserved ejection fraction (HF-pEF), Cardiac MRI is useful as part

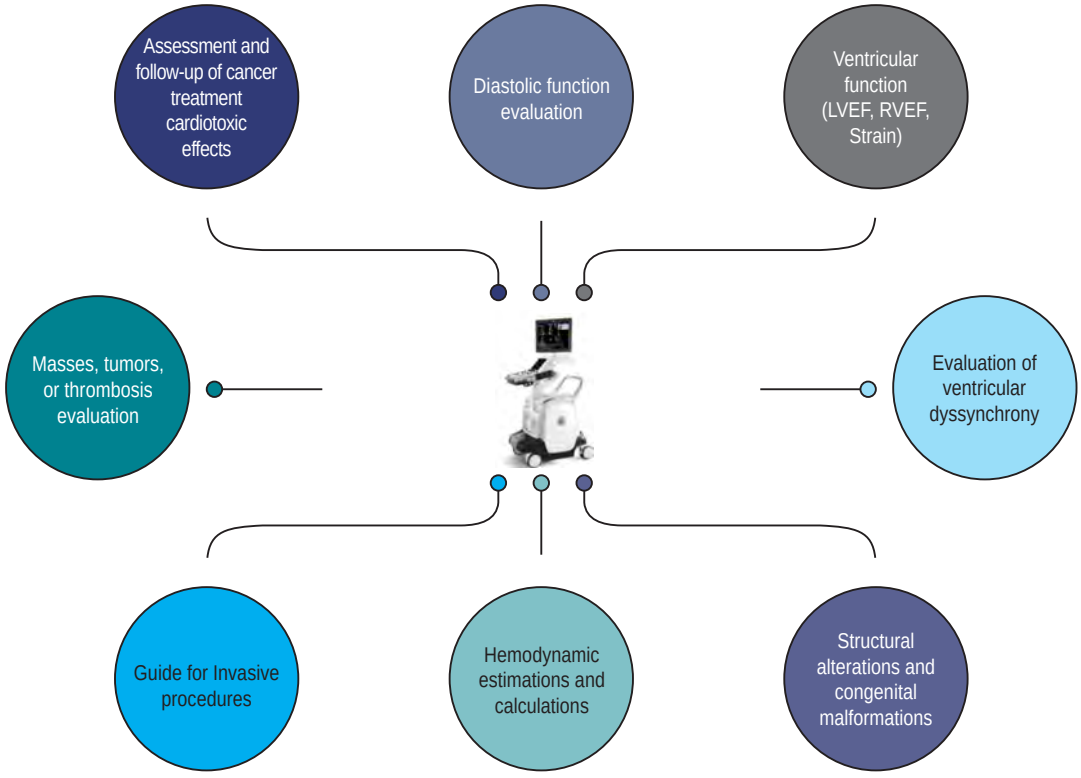


Figure 3:

Echocardiography usefulness in Heart Failure comprehensive approach. LVEF = left ventricular ejection fraction, RVEF = right ventricle ejection fraction.

of advanced diagnosis of diastolic function, although current evidence does not support routine use of Cardiac MRI for diastolic function assessment.

c.5. **Congenital heart disease.**[26,27] Due to its accuracy, it is the first choice method for the study of complex congenital heart disease where an echocardiographic study is insufficient.

c.6. **Ischemia and myocardial viability.**[27] Through stress protocols, Cardiac MRI is able to identify both ischemia and myocardial viability, with precision equivalent to methods such as nuclear cardiology; however, it should be consider the access to this method when studying these parameters.

It should be noted that, despite all these advantages, in Mexico and in developing countries, access to this diagnostic method remains limited, so there is the requirement to ask for it, as well as for the installation of more equipment and the training of specialized medical personnel to perform Cardiac MRI in most states of the country. Another limitation are patients carrying medical devices which are not compatible with Cardiac MRI, such as old pacemakers or metal prostheses, so in the immediate future consideration should be given to privileging the use of devices that are compatible with the resonator, as the likelihood that a patient will require an increasing MRI during their lifetime.

It is therefore recommended that ***any structured program for the comprehensive management of HF must have access to the Cardiac MRI***. In individual cardiological practice, the use of this method should be considered for the study and characterization of patients with cardiomyopathies, where echocardiographic diagnosis is not sufficient, as well as in patients with severe involvement of right ventricle.

4. Nuclear medicine[28,29]

Nuclear medicine in the HF approach has been rethinked in recent years due to the development of new non-invasive imaging techniques. High cost and exposure to ionizing radiation are two of the main limitations for its use. In addition, the results of the STICH study generated controversy regarding the usefulness of this imaging technique; however, its usefulness in certain cases for the study of viability and/or myocardial ischemia is undeniable, so in certain cases of Ischemic HF, its usefulness has already been proven. On the other hand, in cases with suspected Transthyretine amyloidosis, ^{99m}Tc-DPD scintigraphy and SPECT/CT could be a helpful tool.

Therefore, ***it is advisable to rationalize the use of nuclear medicine techniques when other noninvasive imaging methods are inconclusive*** and the study by this method is necessary for therapeutic decision-making that may change the prognosis of patients.

5. Invasive hemodynamics and cardiac catheterization[16]

Hemodynamic studies are essential in certain clinical scenarios, in ischemic patients, coronary angiography continues to be the Gold standard for defining coronary anatomy, additionally, methods for the study of coronary anatomy and physiology such as intracoronary ultrasound or fractional flow reserve estimation (FFR) provide additional information that is essential for decision-making, in cases where the single angiographic imaging is not able to generate diagnostic conclusions.

In addition, invasive hemodynamics plays a key role in the study of cardiovascular physiology by providing relevant information regarding the taking of intracardiac pressures, calculation of hemodynamic parameters such as cardiac output (CO), pulmonary capillary pressure (PCP), pulmonary resistances (PR), among others. These parameters are indispensable in the comprehensive study of patients with pulmonary hypertension or in those in cardiac and/or pulmonary transplant protocols.

Recently, the use of invasive hemodynamic parameters in the comprehensive study of some patients with HF-pEF has become relevant in certain centers of excellence in heart failure management and provide additional information for scientific research purposes.

It is therefore recommended that centers specialized in the management of HF and pulmonary hypertension have access to studies and procedures of invasive hemodynamics and interventional cardiology.

Figure 4 summarizes the route and elements for diagnosing HF as well as the suggestion of medical personnel involved in this process.

6. Evaluation of the functional class and clinimetrics

Evaluation of the functional class in HF can be a challenge for the clinician, especially in seemingly stable patients who report light symptoms during questioning. This is largely explained by the fact that many patients self-limit the intensity of actual symptoms. Therefore, in those where there is doubt about the true functional class, it is advisable to use elements that allow the burden of symptoms to be objective, particularly with regards to effort dyspnea.

The 6-minute walk test (6MWT) has been presented as the best option to assess the functional class of patients with HF.[30] This study does not require high technology and is cost-useful. Its main parameter is the distance traveled for 6 minutes of walking flat, in a specifically designed lane to avoid obstacles. An increase in the distance travelled by 30 meters or more, after an intervention, is considered as a good therapeutic response. On the other hand, the drop of 4% or more in peripheral oxygen saturation during the study is a marker of poor prognosis. Therefore, ***it is recommended that every patient entered in a structured program for HF management, be considered to perform a 6MWT*** in order to have objective information of its functional class and be able to monitor the clinical response to the established treatment.

On the other hand, clinimetry is a complement to semiology and allows us to know the effects of symptoms on each individual patient. This is relevant, as the impact of dyspnea can be significantly different on a young person who is active, against an elderly patient without productive activities; hence the need to measure the impact of symptoms on each subgroup of patients.

There are tools that, through specific questionnaires, explore the burden of disease and link symptoms to the quality of life of patients by exploring aspects such as physical limitations, frequency and stability of symptoms, self-care and social limitations among others.

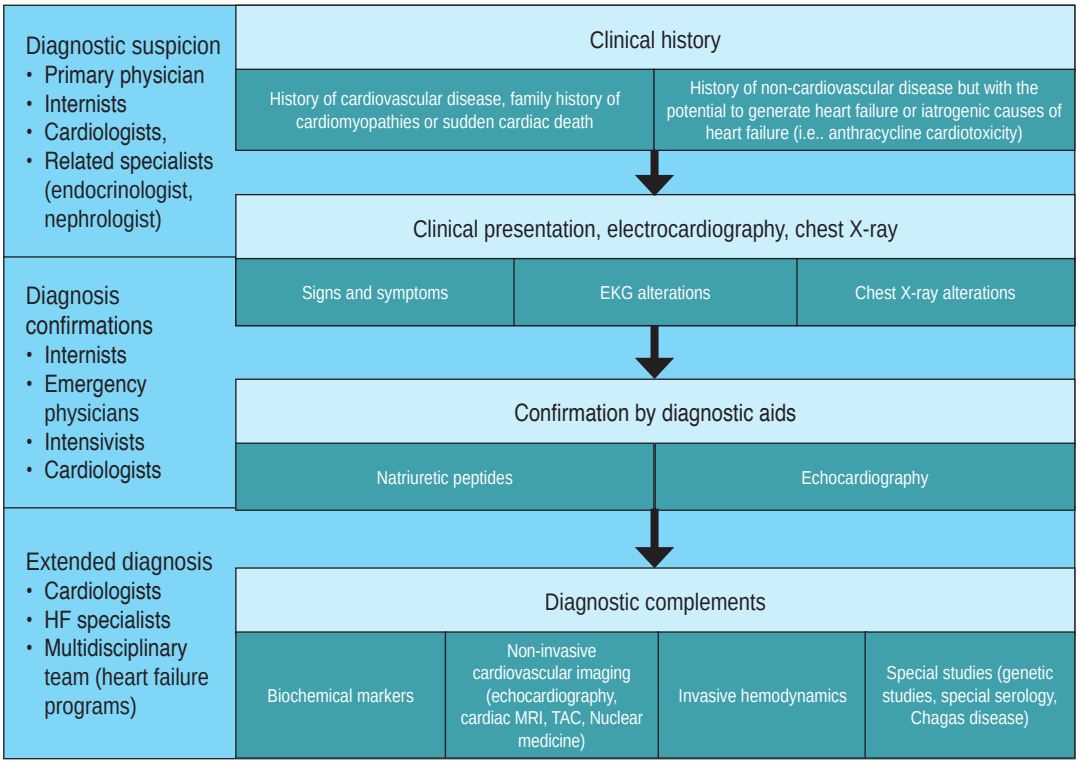


Figure 4:

Heart failure diagnostic pathway.

Table 6: Heart failure Domains explored by clinimetric questionnaires.

Questionnaire	Number of items	Evaluated dimensions	Comments
Minnesota living with heart failure questionnarie (MLWHFQ)	21	• Physical dimension (0-40 points) • Emotional dimension (0-25 points) • Global dimension (0-105 points)	• This is the most used tool for the quality of life evaluation in patients with chronic heart failure
Kansas city cardiomyopathy questionnaire (KCCQ)	23	• Physical limitation • Symptoms (stability, frequency and seriousness) • Self-care • Quality of life • Social limitation	• Each dimension has a theoretical range of 0-100 • Two scores are calculated: • Clinical summary • General summary • This is the recommended instrument by the ICHOM (International Consortium for Health Out-comes Measurement) and is used to evaluate the QoL in all contemporary clinical trials
EQ-5D	15	• Mobility • Self-care • Daily activities • Pain/malaise • Anxiety/depression	• Additionally, includes a visual analogue scale from 0-100 for the self-evaluation of the patient well-ness perception at the time of the questionnaire

Among the most commonly used and recommended are the Minnesota *Living with Heart Failure* Questionnaire (MLHFQ)[31] and the University of *Kansas City Cardiomyopathy Questionnaire (KCCQ)*.[32] Both instruments have been validated internationally and are even recognized as a pillar to assess quality of life in all contemporary clinical trials in HF. In addition, the European proposal is found with the EQ5D[33] questionnaire that explores 5 domains in patients, including: mobility, self-care, limitation for daily activities, the presence of pain or discomfort, as well as psychological aspects such as anxiety or depression associated with the health problem *(Table 6)*.

Therefore, ***it is recommended that every patient within a structured program for HF management be evaluated with clinimetric scales such as Minnesota (MLWHFQ), Kansas (KCCQ) or EQ-5D questionnaires.***

7. Prognotic stratification

As long as HF is a condition with poor prognosis in the medium and long term, it is essential to have tools that allow to know, as accurately as possible, the risk level of each patient in order to implement the most appropriate recommendations to achieve a comprehensive treatment.

Clinical information and information derived from diagnostic aids have been integrated into several models and proposals of prognostic stratification scales at the global level. Among the most recognized are the HFSS scale *(Heart Failure Survival Score)*[34] and the MAGGIC scale (*Meta-Analyisis Global Group in Chronic Heart Failure)*,[35] in both cases the risk of short- and *medium-term* mortality is explored in *Table 7*. While there is no specific prognostic stratification scale in Mexico, ***it is recommended that every patient admitted to structured programs for the HF management have a risk stratification*** as part of their initial approach and follow-up.

III. TREATMENT

HF treatment should be timely, comprehensive, multidisciplinary, and as far as possible individualized.

Therapeutic goals should go beyond the improvement of symptoms, and should impact

syndrome physiopathology in order to prevent disease progression and decrease major outcomes such as hospitalizations and death. Additionally, the new paradigm is to overcome the cardiocentric approach to generate comprehensive patient-centered management in which the treatment of HF-associated comorbidities should be considered systematically. Finally, it is important to consider palliative management for patients with advanced stages who are not candidates for disease-modifying treatments or where they are insufficient *(Figure 5)*.

In order to achieve these objectives, it is necessary to consider multiple interventions that include the treatment of the causal entity, non-pharmacological management, comprenhensive pharmacological therapy, invasive management (surgery and interventions), the rational use of devices like cardiac resinchronization therapy (CRT) and implantable cardiac defibrilators (ICDs), electrophysiology procedures, as well as mechanical circulatory assistance *(Figure 6)*. Recommendations for the HF-rEF syndrome management are described below, as HF-pEF will be addressed in a special section.

III.1 Non-Pharmacological treatment

Non-pharmacological measures should be considered an essential part of comprehensive management regardless of the HF etiology and classification.

Its systematic application improves the functional class, quality of life and have a positive prognosis impact. Additionally, they are cost-effective.

Basic interventions should include:

1. **Sodium Restriction.**[36-39] Sodium (Na^+) is essential for life; however, an excess in its intake in patients with HF is associated with worsening symptoms for both, pulmonary and systemic congestion. On other hand, a severe restriction (180 mg/day or less daily) of sodium has been associated with adverse outcomes including an increased mortality. Therefore, while the ideal amount of sodium intake per day in HF has not been defined in multicenter studies, it is ***accepted that a total intake of 2-3 g of sodium per day is safe***

Table 7: Heart failure prognostic scales.

Heart failure survival score (HFSS)	MAGGIC Score
• Coronary arterial disease (Yes = 1, No = 0, (X 0.693) ± • Intraventricular conduction delay (Yes = 1, no = 0 X 0.6083) ± • Left ventricular ejection fraction (LVEF) …. X 0.0470, ± • Heart rate (LPM) ….X 0.0216, ± • Serum sodium (mEq/L) …. X-0.0470, ± • Mean blood pressure (mmHg), …. X-0.0255, ± • Maximum oxygen consumption (MvO_2), …X -0.0546	• Age (years) • LVEF (%) • Systolic blood pressure (mmHg) • Body mass index (kg/m^2 SC) • Creatinine (mg/dL) • NYHA functional class • Gender • Smoking • Diabetes • COPD • HF diagnosis > 19 months • Use of betablockers • Use of ACEIs/BRAs
• High risk < 7.19 pts (1 year survival of 35%) • Intermediate risk 7.2-8.09 (one-year survival of 60%) • Low risk > 8.10 (one-year survival 88%) • Difficult to get the MvO_2	Death risk estimation at one and three years Preferred scale for patients with heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, HF = heart failure.

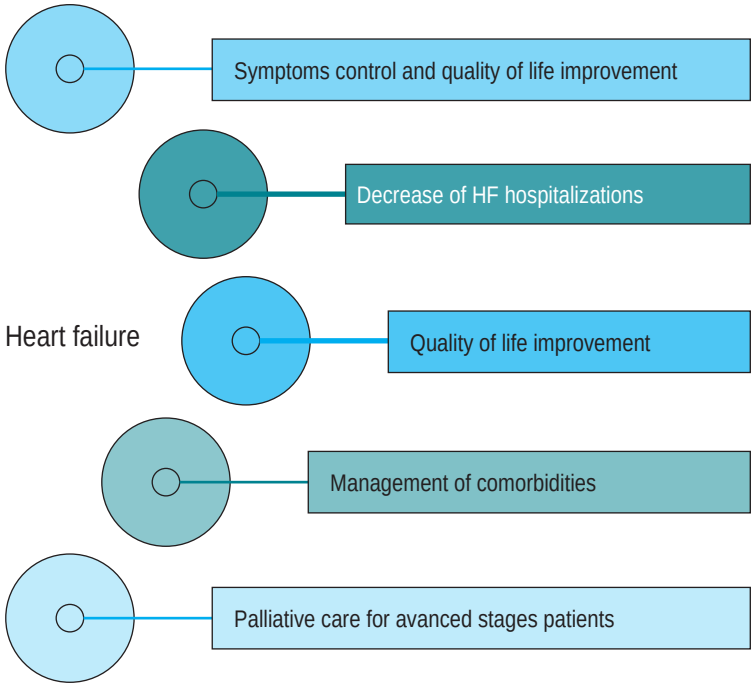


Figure 5:

Heart Failure therapeutic goals.

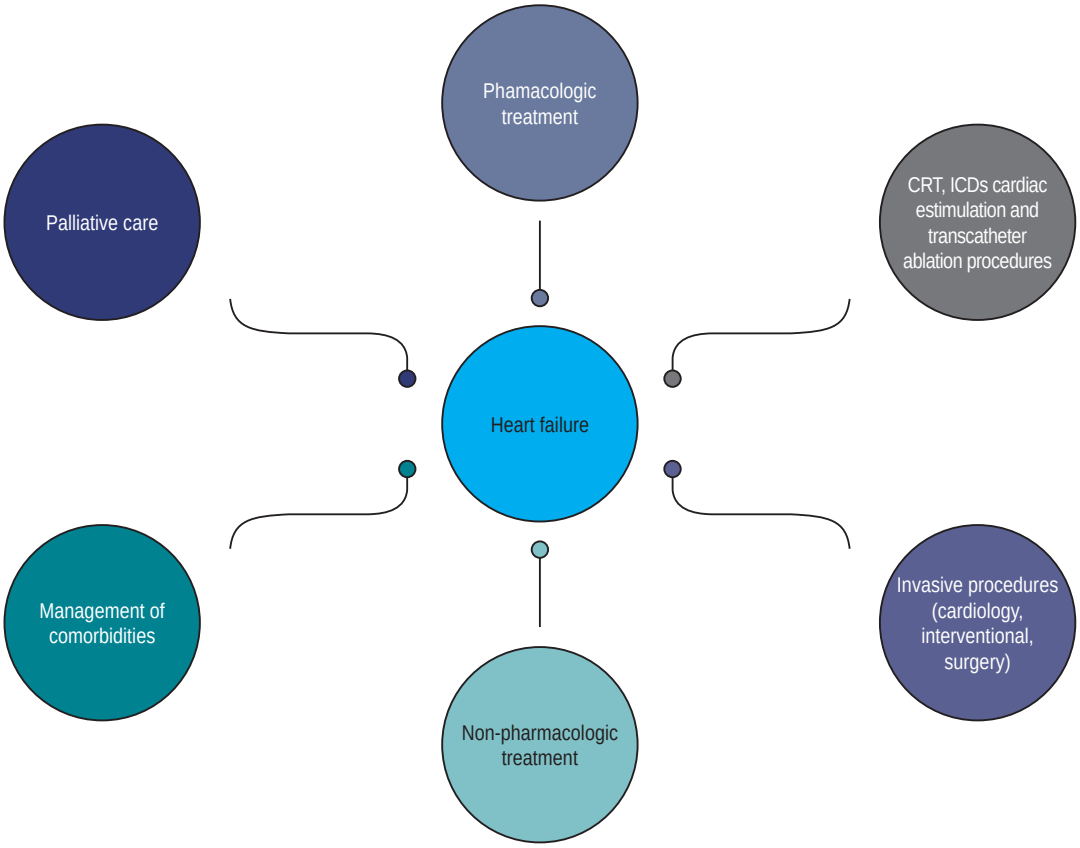


Figure 6:

Heart failure comprehensive treatment.
CRT = cardiac resynchronization therapy,
ICDs = implantable cardiac defibrillators.

and feasible to achieve. It is recommended to remove from the diet foods or drinks rich in salt such as sausages, gasified beverages and prepared or industrialized meals.

2. **Nutrition.**[40-44] ***There is no universal diet for patients with HF; however, it is accepted that a cardiac-healthy schemes such as the Mediterranean diet and the American DASH model could be adopted in most patients with HF***. In those, the consumption of natural foods, vegetables and fiber is recommended and the refined sugars intake is limited. It is important to perform an individual nutritional assessment as part of a structured program for the HF management and to adapt the recommendations for each particular case. Patients with cardiac cachexia or biochemical malnutrition data should be identified since they are considered as vulnerable population at high risk of additional complications. Otherwise, obesity is an added problem that has an impact on HF symptomatology. Despite this, there is no conclusive evidence to indicate that intensive obesity treatment has a significant impact on HF prognosis; however, ***it is recommended that nutritional advice in HF include obese patients management,*** particularly those in morbid grade or with aggregated situations (e.g. Metabolic syndrome).

   Routine consumption of dietary supplements including vitamins is not recommended. This is in order to avoid a treatment disease interaction. However, if the nutritional assessment detects a specific deficiency of any vitamin or oligoelement, they may be supplemented individually.

3. **Liquid consumption.**[4,16,45,46] One of the most prevalent clinical data in HF is water retention. ***An excess in fluid consumption is associated with acute decompensation of HF so it should be avoided.*** Additionally, an increase in water consumption is associated with electrolyte imbalance with dilutional hyponatremia that could be potentially severe. In this regard, it is recommended that total daily fluid intake should not exceed 2 liters for patients with Functional Class I (NYHA) and 1.5 L/day in patients with Functional Class II, the above is equivalent to 30-35 mL/kg bodyweight per day. In decompensated patients or with advanced HF, intake should be individualized according to each specific clinical scenario and modified according to therapeutic response.

4. **Physical activity and cardiac rehabilitation.**[4,16,46-51] Under a traditional conception, patients with HF had to rest most of the time; however, targeted physical training is shown to improve the functional class, perception of well-being and vital capacity of patients. Studies such as HF-ACTION (The *Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training)* strongly demonstrated the benefits of physical activity in patients with HF-rEF including hard outcomes such as an 11% decrease in overall mortality or hospitalizations for any cause (P=0.03). Therefore, in this positioning ***it is recommended that every patient with stable HF, initiate a physical activity program***. Ideally, patients should be referred to cardiac rehabilitation programs, but in the absence of such services in Mexico, to initiate physical activity guided by the treating physician as long as he has the professional skills to guide this process would be the option. It is important that patients are supervised so responsibility cannot be delegated to gyms or non-professional trainers.

5. **Psychological evaluation and intervention.**[52-54] Dysthymia, depression, and other neuropsychological disorders are common in patients with HF and their presence negatively affects clinical evolution and prognosis. Therefore, patients should be evaluated in this regard and ***in the face of the detection of any indication of psychological or psychiatric pathology added, patients with HF should be referred to mental health services***. As depression is the most common psychopathology in HF, the use of PHQ-2, PHQ-9 or Beck Depression Inventory (BDI) are recommended as screening tools for the identification of depression in these patients.

6. **Education for patients and family members.**[16,55-57] Patient, relatives and caregivers empowerment is indispensable to achieve a good therapeutic adherence

and to optimize the results of treatment. All educational measures aimed at improving disease awareness, drug management, recognition of alarming data, should be considered within an HF educational program.

Figure 7 summarizes non-pharmacological measures for the management of HF.

III.2 Drug treatment

In patients with HF-rEF, proper drug use is the cornerstone of treatment. The role of each pharmacological agent has now been redefined according to its role in achieving therapeutic objectives. From a practical point of view, we have three main categories *(Figure 8)*:

1. Disease-modifying drugs,
2. Medicines for symptomatic control and
3. Drugs for special situations and emerging drugs

1. Disease-modifying drugs

Neurohumoral over expression, understood as a permanent increase of the Renin Angiotensin Aldosterone System (RAAS) activity, and the sympathetic nervous system (SNS) activity, is a ***common condition*** in all patients with HF-rEF and largely defines the natural history and prognosis of the disease. These mechanisms, compensating in principle, are negative when their activity is extended.

Figure 7: Non-pharmacological measures for heart failure treatment.

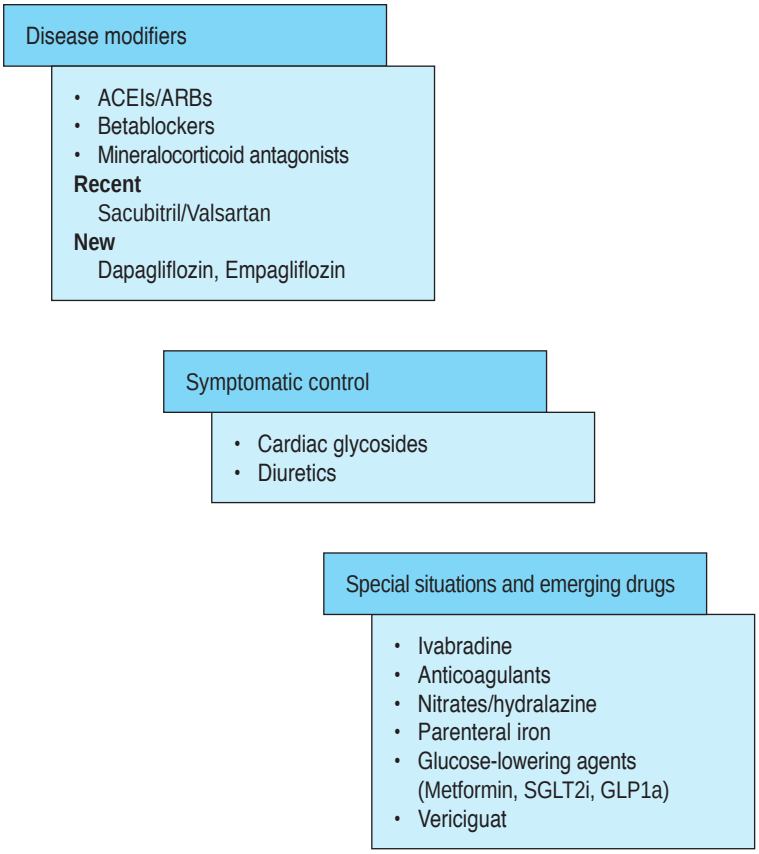


Figure 8: Pharmacologic treatment for heart failure with reduced ejection fraction.

For this reason, ***blocking and modulation of neuroendocrine over expression is a mandatory condition in the patient with HF-rEF***.

The following groups of medicines are available for it:

a. ACE inhibitors (ACEIs)[4,16,58,59]

Initially designed for the management of high blood pressure, its indication for the management of HF was expanded from evidence of seminal studies such as SOLVD-P, SOLVD-T, CONSENSUS, SAVE and V-HeFT. In all of them there was consistency in terms of reducing hard outcomes such as cardiovascular death and hospitalizations by HF. The main representatives are enalapril and captopril, although there is consensus of a class effect medicines such as ramipril, lisinopril, and perindopril are accepted. Currently ***all clinical practice guidelines recommend ACEIs as initial management of HF-rEF.***

b. Angiotensin receptor blockers (ARBs)[4,16,60-63]

A limitation for the use of ACEIs is the presentation of cough as a drug adverse reaction, a situation that is relatively common. Also, patients with angioedema history have an absolute contraindication for the use of ACEIs although this reaction is rare.

For this reason, Angiotensin Receptor Blockers (ARBs) offer an alternative for patients who are intolerant to ACEIs or have a formal contraindication for their use.

The most robust evidence comes from studies such as ELITE II with Losartan, the CHARM program with Candesartan cilexetil, and the VAL-HeFT with Valsartan. In these studies, ARBs were shown not to be inferior to ACEIs in terms of decreased outcomes in patients with HF-rEF. However, since a significant superiority was not shown to not demonstrate a significant superiority ***angiotensin II receptor blockers should be considered as second choice drugs and their use should be considered only in patients with impairment for the use of ACEIs***.

c. Angiotensin receptor antagonists and neprilysin inhibitors[4,16,64-69]

Angiotensin receptor-neprilysin inhibitors (ARNIs) offer a unique alternative to comprehensive modulation of neuroendocrine over expression in HF-rEF. Its mechanism of action not only includes an Angiotensin II blockade, but manage to optimize the biological effects of natriopeptides by inhibiting neprilysin system[64] which results in a significant reduction of hemodynamic overload for the failing heart; in the medium and long term this drugs exert cardioprotective effects that results in improved cardiac remodeling and decreased apoptosis of insufficient cardiomyocytes *(Figure 9)*. Currently Sacubitril/Valsartan is the first and only representative of this therapeutic class.

The PARADIGM-HF[65] study is a double-blinded, randomized, multicenter clinical trial in patients with HF-rEF where Sacubitril/Valsartan superiority was demonstrated in the

prevention of major events (cardiovascular death, HF hospitalizations) when compared to Enalapril. In this study, ARNI reduced the risk to present such events by 20% achieving a high clinical and statistical significance (p = 0.0000004) *(Figure 10)*. This clinical trial is very relevant because for the first time in the contemporary HF history, a drug which is not additional to standard management, but replaces the gold standard of RAAS blocking, was able to demonstrate its superiority.

Among the most important findings of the PARADIGM-HF sub-analysis is the fact that sacubitril/valsartan significantly reduced the risk of sudden cardiac death (SCD)[66] (HR 0.80, CI 95% 0.88-0.94, p = 0.08), a situation that is relevant when neither ACEIs nor ARBs have a significant effect on this outcome.

Recently, studies such as TRANSITION[67] and PIONEER[68,69] demonstrated the safety and efficacy of the early initiation of sacubitril/valsartan in patients with HF during the vulnerable phase, i.e. during convalescence period after a HF hospitalization. It should be noted that both studies looked at a significant patient proportion which, unlike the PARADIGM-HF study, had no prior management with ACEIs or ARBs. In these patients as in those where prior treatment with ACEIs or ARBs were replaced, the use of sacubitril/valsartan was superior to conventional treatment. Hence, the fact that clinical scenarios for the current use of sacubitril/valsartan could be expanded.

Therefore, contemporary clinical practice guidelines recommend the use of Sacubitril/Valsartan as a fundamental part of a disease-modifying treatment. From this positioning and derived from scientific evidence, ***it is recommended that whenever possible, sacubitril/valsartan should be considered as the preferred option for modulation of renin angiotensin system in patients with HF-rEF***. In patients during the vulnerable period of HF (pre-hospital discharge of an Acute Heart Failure episode or weeks after hospital discharge), Sacubitril/valsartan should be considered as first line for the Angiotensin Renin System modulation.

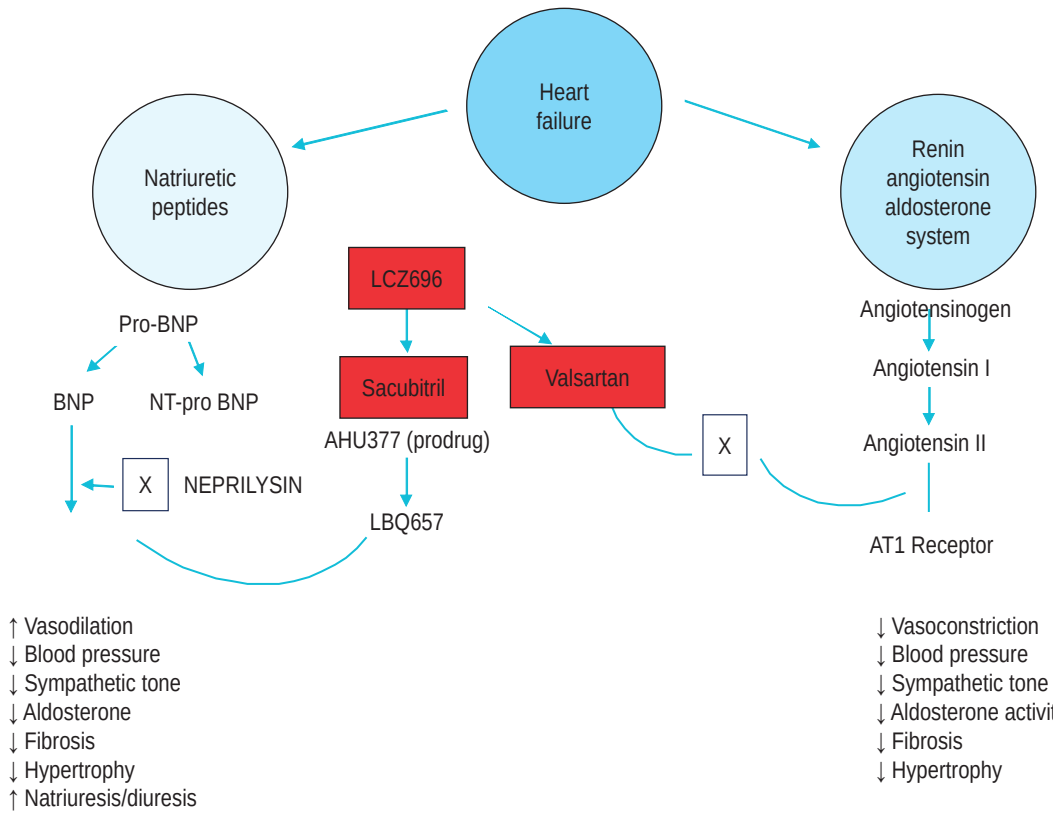
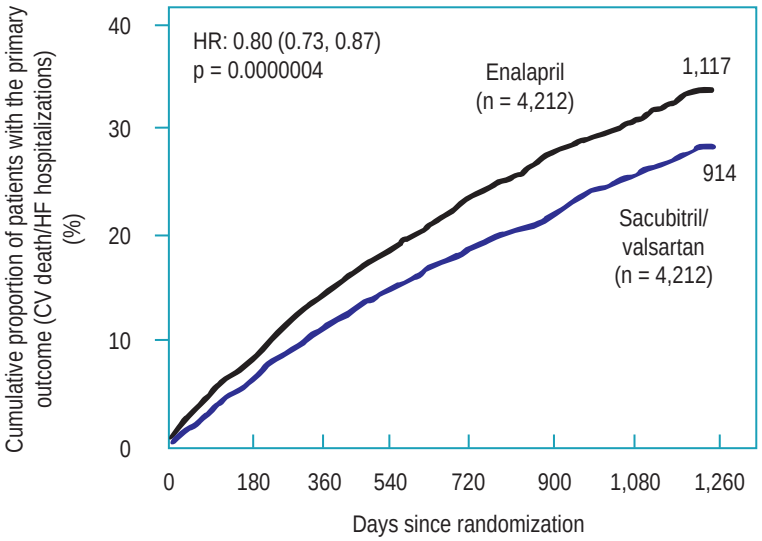


Figure 9:

Mode of action for renin angiotensin antagonists and neprilysin inhibitors (ARNIs).



At risk

Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236
Sacubitril/ valsartan	4,212	3,922	3,663	3,018	2,257	1,544	896	249

Figure 10: Sacubitril/valsartan effects on HF major cardiovascular outcomes with reduced ejection fraction. Source: McMurray JJV et al.[65]

Figure 11 shows the proposed start-up and up-titration protocol for the appropiate use of ACEis, ARBs and ARNIs in HfrEF patients.

d. Beta blockers (BBs)[4,16,70-75]

The use of Beta blockers in HF began in the 70s; however, it was not popular until 20 years later. The reasons were the atavic concept of its negative inotropic effects and the belief that tachycardia could be beneficial in patients with HF. However, **ALL** original studies have uniquely demonstrated the benefit of adding beta blockers to renin-angiotensin antagonists in terms of reducing cardiovascular deaths and HF hospitalizations. Moreover, beta blockers reduce the risk of sudden cardiac death in patients with HF. Even in patients with NYHA functional class IV HF, carvedilol demonstrated its superiority over placebo in reducing the risk of major cardiovascular outcomes. This is explained by its effects on heart rate control, reduced hemodynamic overloads and neuroendocrine control in HF.

It is important to emphasize two aspects for the safe use of Beta blockers in HF, the first is to use drugs that have prove useful, such as carvedilol or bisoprolol; in the case of metoprolol, metoprolol succinate should be used and not tartrate. With regard, Nebivolol, this drug could be consider, but the evidence is not as robust as with the drugs already mentioned and in addition its larger vasodilator effect makes its titration more complex so it should not be considered as the preferred option for HF management. Medications such as Propranolol or Atenolol are not indicated for HF management. Second aspect is to start with the lowest possible dose and titrate according to heart rate and blood pressure numbers (see beta blocker dose titration scheme, *Figure 12)*.

From this positioning it is recommended that ***every patient with HF-rEF should be managed initially with a beta blocker*** along with AARS antagonists in order to reduce the risk of cardiovascular death, sudden cardiac death and HF hospitalizations.

Unfortunately, the systematized use of beta blockers in HF is scarce in everyday clinical practice, so it will be necessary to encourage its ***use in HF-rEF according to indications currently accepted.***

e. Mineralocorticoid receptor antagonists[4,16,76,77]

Mineralocorticoid receptor antagonists (MRAs) also known as antialdosteronics are medicines that were initially used as potassium-sparing diuretics, and in this sense as adjuvants to loop diuretics. However, their diuretic potency is limited, and their use can be risky in patients with hyperkalemia or advanced kidney disease.

In HF, the RALES[76] study redefined the usefulness of MRAs by demonstrating that Spironolactone was able to reduce the risk of CV death in 30%, and sudden cardiac death in a cohort of patients with HF-rEF previously treated with ACEIs and digoxin. However, this study only included patients with severe HF (average LVEF 25%, NYHA FC III-IV) so initially the recommendation was limited to patients in this clinical context. A decade later, the EMPHASIS[77] study showed that beneficial effects of antialdosteronics could be extended to patients with non-severe HF-rEF, finding that the addition of Eplerenone to standard

treatment decreased the risk of CV death, sudden cardiac death and HF hospitalizations in up to 37% (HR 0.63, CI 95% 0.54-0.74, p < 0.001), the difference between this and the RALES study lies in the type of patients, as well as on the treatment previously received, particularly the proportion of beta blockers use (86% in EMPHASIS vs 10.5% in RALES). These differences are important as they expand the indication of antialdosteronics to all symptomatic patients with HF-rEF.

The use of antialdosteronics with angiotensin renin system antagonists and beta blockers is recommended as initial pharmacological management of patients with HF-rEF to maximize the benefits of a triple neuroendocrine blockade therapy.

It should be emphasized that precautions are to be exceeded with their use in order to avoid renal function deterioration and hyperkalemia.

f. New evidence of disease-modifying drugs

Recently, some medicines have been added, without having a definitive conclusion on their action mechanism in terms of cardiovascular protection, in the evidence, have shown a significant role in modifying the clinical course of the cardiovascular disease and its outcomes. Examples of the above are dapagliflozin and empagliflozin.

Dapagliflozin. Dapagliflozin belongs to sodium-glucose co-transporter-2 inhibitors (SGLT2i), a group of drugs that were initially designed for glucose control in patients with Type 2 Diabetes which action mechanism based on decreasing renal glucose reabsorption. In original studies with agents of this therapeutic class (empagliflozin, canagliflozin and dapagliflozin),[78-80] their effect as glucose-lowering agents was confirmed, but a

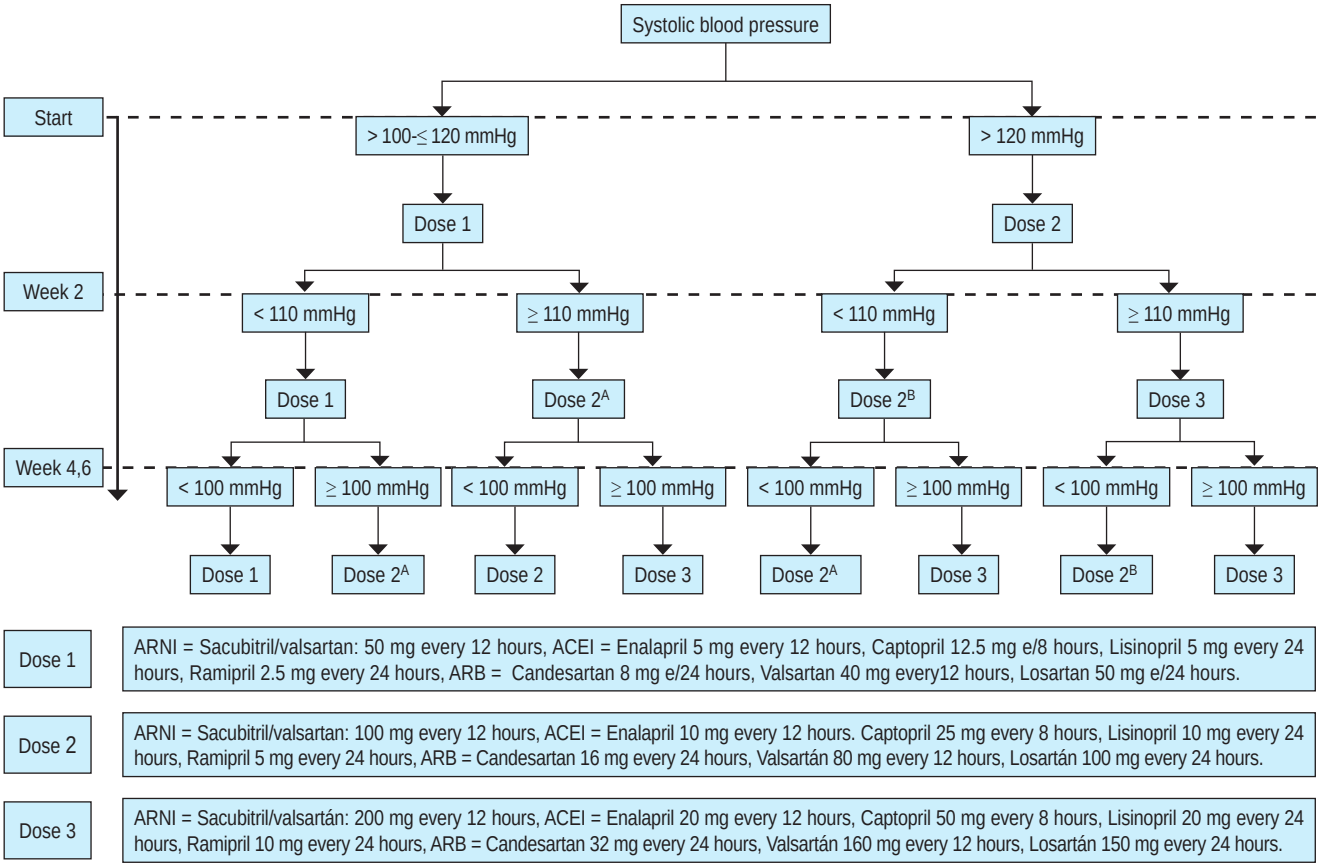


Figure 11: Proposed titration scheme and dose optimization of renin angiotensin system antagonists according to baseline systolic blood pressure values.

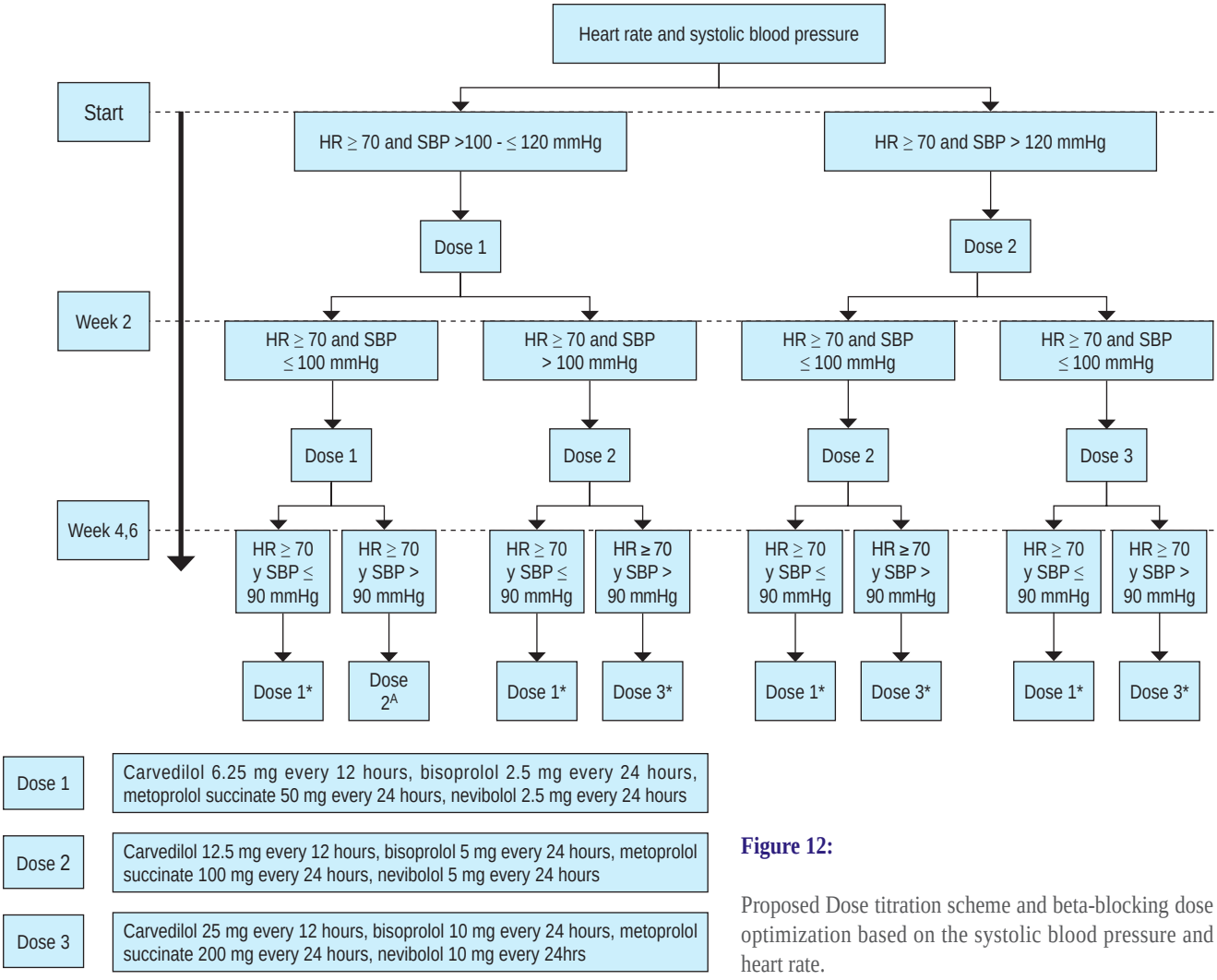


Figure 12:

Proposed Dose titration scheme and beta-blocking dose optimization based on the systolic blood pressure and heart rate.

remarkable cardiovascular safety profile was also demonstrated, and particularly an outstanding fact was the reduction of HF hospitalization risk. This observation raised the hypothesis about a potential cardioprotective effect of these therapeutic agents, particularly regarding HF.

Based on the above, studies have been designed in HF populations with the aim of intentionally exploring the effect of these drugs on hard outcomes from a cardiovascular point of view. The DAPA-HF trial *(Dapagliflozin in patients with Heart Failure with Reduced Ejection Fraction)*[81] is a multicenter, multinational clinical trial in which 4,744 patients with symptomatic HF-rEF, NYHA functional class II-IV were studied, with the primary objective of demonstrating that the addition of dapagliflozin to standard pharmacological therapy was superior to placebo to decrease the combination of cardiovascular death and/or heart failure worsening, HF hospitalizations and/or visits to emergency services for intravenous treatment of HF. In this study two important aspects were highlighted, firstly the sample included patients with and without diabetes, secondly, in the vast majority of cases, the patients had optimized treatment according to the latest clinical practice guidelines recommendations. Study results demonstrated a favorable effect of the addition of dapagliflozin to standard management by reducing the risk of primary final outcome by 26% (HR 0.74, CI 95% 0.65-

0.85, p < 0.001) regardless of the presence of diabetes, prior treatment, age, gender and LVEF. These results led to the extension of indication for the use of dapagliflozin in the United States and currently Food and Drug Administration (FDA) accepts the use of dapagliflozin to reduce the risk of cardiovascular death and/or cardiac failure hospital stays in patients with HF-rEF regardless of their diabetic status. Therefore, beneficial effect of dapagliflozin as part of HF treatment regardless diabetes history is concluded. It is recommended to consider dapagliflozin as another element for HF-rEF therapeutic optimization process.

The EMPEROR-HF *(Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure)*[82] study was the second clinical trial to test SGLT2i efficacy and safety in a population of patients with HF-rEF regardless of the presence of type 2 diabetes. This study included 3,730 patients with HF-rEF who were randomized to receive empagliflozin 10 mg/day or placebo in addition to standard heart failure treatment. The primary outcome was the combination of cardiovascular death/hospitalizations due to HF worsening. Secondary outcomes highlighted the frequency of eGFR decrease between both treatment groups. EMPEROR-HF study results demonstrated a beneficial effect in favor of empagliflozin over placebo with a decrease in risk rate for the primary outcome of 25% (HR 0.75, 95% CI 0.65-0.86, p < 0.001), this effect was mainly conditioned by the decrease in the number of hospitalizations due to HF exacerbation (HR 0.70, 95% CI 0.58-0.85, p < 0.001) than reducing CV death (HR 0.92, 95% CI 0.75-1.11, p = NS). As a highlight, a very significant protective effect on renal function was seen when patients with empagliflozin had a lower proportion of renal impairment compared to placebo (0.50, 95% CI 0.32-0.77, p < 0.01). These results were independent of diabetic status or absence of diabetes. It should be noted that in the EMPEROR-HF study the population had high baseline NT-proBNP levels (-1800 pg/mL); it is also the first study in which about 20% of the population was treated with ARNIs and additionally 1 in three patients were carriers of an implantable defribrillator. These data could influence the CV death outcome; however, this conclusion will come after in-depth data analysis and *post hoc* studies results.

Evidence of the cardioprotective effect of SGLT2i is robust and allows them to be considered as part of therapeutic optimization process for patients with HF-rEF beyond their role as glucose-lowering drugs; the indication expands to non-diabetic patients population. Therefore, ***it is suggested to consider dapagliflozin or empagliflozin as drugs that optimize HF-rEF treatment regardless of DM2 presence.*** It is important to emphasize that ***SGLT2i do not replace RAAS antagonists, ARNIs or bletablockers in HF-rEF,*** so they should only be considered when a patient has already received the standard management. In addition, it is recommended to adhere to the recommendations and schemes of the main clinical studies with iSGLT2 as well as to the indications approved by the regulatory agencies of each country.

While it is true that canagliflozin demonstrated same potential effect in initial trials, such studies were limited to DM2 population, with low chronic HF prevalence, and HF was an exploratory and secondary objective. Therefore, at this time, the use of Canagliflozin should be restricted ***to DM2 patients*** with high CV risk or with diagnosed CV disease, including HF, as a treatment to improve metabolic control, renal function and to reduce CV death or HF hospitalization risk.

Finally, it should be noted that despite the positive results, it is still not yet defined the exact mechanism or mechanisms through which these drugs exert their positive effects on HF patient, so an extensive series of studies aimed at defining this question is underway; however, clinical outcomes are significant, and the lack of a mechanistic explanation should not be an obstacle to their use on the basis of proven clinical evidence.

2. Medicines for symptomatic control

There are a several drugs that have been shown to be useful for the symptomatic relief in patients with HF; however, they have been insufficient in terms of their actual ability to change the disease natural history and consequently in a decrease of hard outcomes. Within these drugs we find predominantly diuretics and digoxin.

Diuretics are very useful for managing symptoms from water retention. In HF these symptoms are very common and are in fact an essential part of clinical picture of a large number of patients. The use of diuretics, mainly those acting on loop of Henle (Furosemide, Bumetanide, Torasemide) have been a constant on HF patients treatment, in both settings hospital and ambulatory care. However, its chronic and high-dose use has been associated with adverse outcomes as hydroelectrolytic imbalance. Moreover, in patients with volume depletion, the dose titration process of disease-modifying drugs becomes difficult and it is common that in this case, patients do not receive appropriate doses. For this reason***, this positioning recommends limiting the use of diuretics for patients with symptomatic HF with fluid retention evidence.*** Prolonged use of high doses of diuretics in stable patients without evidence of fluid retention should also be avoided. Finally, it is recommended to follow and monitor patients under diuretic management from both points of view, clinical and laboratory, including the quantification of serum and urinary electrolytes.[4,83]

Digoxin is the oldest formal drug for HF management. Its positive effects in terms of symptomatic improvement are undeniable.[84] In addition, the effects for heart rate control in patients with atrial fibrillation are also relevant.[85,86] However, like diuretics, contemporary evidence has not been able to demonstrate the superiority of digital drugs in terms of decreasing mortality in HF.[87] Additionally, its therapeutic range is narrow so patients who use it should be monitored in order to reduce the risk of intoxication. Therefore, ***it is recommended to limit the use of digoxin*** to patients with HF-rEF whose symptoms persist despite the use of disease-modifying and diuretic drugs ***and not to consider digoxin as HF initial management.*** It is also recommended to use low doses and as far as possible perform periodic monitoring of the electrocardiogram and digital serum levels.[4,16]

3. Drugs for special situations and emerging drugs

There are specific situations that justify the use of drugs that have been shown to be helpful in reducing the morbidity of patients with HF-rEF. The most commonly used are Ivabradine and the combination of nitrates with hydrazine.

Heart rate (HR) has been shown to be a therapeutic target in HF-rEF. A HR above 70 BPM increases the risk of adverse outcomes in patients with left ventricular dysfunction and HF. While it is true that beta blockers have a fundamental effect on the HR control in HF, indeed, it is often not enough to reach the control target of 70 bpm or less.[88] Ivabradine is a drug which specific function is to exert a selective blockage of the I_f current in sinus node; this conditions a HR reduction without effects on inotropism or vascular resistances.[89] SHIFT study showed that the addition of Ivabradine to standard treatment was able to reduce the risk of HF hospitalizations in up to 26% in HF-rEF patients in sinus rhythm and HR > 70 bpm, Ivabradine reduced the risk of HF death. These results reinforced the importance of controlling HR to a therapeutic target of 70 bpm or less in all patients with HF-rEF.[90] Therefore, in this consensus, ***the use of ivabradine is recommended in any patient with symptomatic HF-rEF who is in sinus rhythm and who despite the use of beta blockers is not able to maintain a resting HR control goal of 70 bpm***. The decision to add Ivabradine should be made in the short term after the initiation of beta blocker therapy in the absence of HR control with beta blockers optimal dose or in those who have not been able to titrate BBs dose for HR control. It is important to note that this medicine is not currently recommended in patients with persistent or permanent atrial fibrillation; on the other hand, it should not be considered as the first option for HR control, except in cases where there is a formal contraindication for the use of beta blockers.

In patients with advanced HF-rEF who despite the use of triple neuroendocrine, diuretic, and digital control therapy and HR on the therapeutic goal, the addition of the combination of nitrates with hydralazine due to evidence of its beneficial effects in this specific scenario could be an option.[4,91,92] This is particularly relevant in patients of African descent as it is the sub.group that has been mostly studied in this regard. Like Digoxin, this combination should not be considered for initial management of HF-rEF.

HF is a clinical condition that is often associated with the development of thrombotic or thromboembolic complications. This has led to the use of anticoagulants is a common practice within the comprehensive management of Heart Failure; however, the use of anticoagulants should be rationalized and limited to specific situations. ***In this regard, patients with HF and atrial fibrillation with a rating of one or more points on the CHAD2DS2-VASCor[4,6,93] scale should be considered for oral anticoagulation management as long as there is no formal contraindication for their use.*** In patients with HF in sinus rhythm HF, the benefits of anticoagulant therapy are controversial, particularly from the results of studies such as WARCEF,[94,95] however, HF is a disease characterized by a high thrombogenic profile, so in patients with intracavitary thrombosis or systemic embolism (e.g. Cerebrovascular disease), in those with severe myocardial damage and alterations of ventricular mobility (dyskinesia), in the presence of structural alterations such as aneurysms or pseudoaneurysms, and in patients at high risk of venous thromboembolism, the onset of oral anticoagulation should be considered by the risk-benefit assessment of such intervention. ***When deciding to initiate oral anticoagulation in HF patients, it is suggested to consider direct anticoagulants as a preferred option,*** because they have shown to be as effective as vitamin K antagonists but safer than these; however, the recommendation should adhere to accepted indications for such drugs.

It is important to note that the pharmacological treatment of the patient with HF-rEF is the result of careful construction involving the addition of several drugs, and not a single principle alone[96] *(Table 8)*.

Figure 13 summarizes the proposed pharmacological treatment of patients with HF-rEF without type 2 diabetes. It is proposed to consider management the triple combination of neuroendocrine control drugs as first-line. This is due to evidence of its complementary benefits. It also proposes the early incorporation of new therapeutic alternatives such as SGLT2i based on the results of recent studies. It is worth emphasize the following:

a. The philosophy behind this scheme is to **provide the *best treatment in the shortest possible time.***
b. Therefore, decision-making for the implementation of integral management must be expedited and in accordance with structured protocols of initiation and dose titration *(Figures 11 and 12)*.

Table 8: HF-rEF Pharmacological treatment evolution.

Drugs	All-cause mortality	Cardiovascular mortality	All-cause hospitalization	Hospitalization for heart failure
ARNI+BB+MCA	0.38 (0.20-0.65)	0.36 (0.16-0.71)	0.58 (0.36-0.92)	0.27 (0.07-1.07)
ACEi inhibitors+BB+MCA+IVA	0.41 (0.21-0.70)	0.41 (0.19-0.82)	0.58 (0.36-0.92)	0.25 (0.07-0.99)
ACEI+BB+MCA	0.44 (0.27-0.67)	0.45 (0.25-0.75)	0.65 (0.45-0.93)	0.34 (0.13 (0.91)
ARB+BB	0.48 (0.24-0.86)	0.50 (0.19-1.12)	0.79 (0.47-1.21)	0.31 (0.07-1.29)
ACEI+BB	0.58 (0.42-0.73)	0.56 (0.37-0.75)	0.75 (0.54-0.92)	0.34 (0.17-0.56)
ACE inhibitors +MCA	0.58 (0.36-0.90)	0.56 (0.31-0.95)	0.69 (0.45-0.96)	0.36 (0.12-0.96)
BB	0.58 (0.34-0.95)	0.62 (0.27-1.32)	0.86 (0.59-1.18)	0.45 (0.13-1.39)
ACEI	0.84 (0.67-1.01)	0.81 (0.60-1.04)	0.89 (0.81-1.05)	0.52 (0.32-0.76)

BB = betablockers, ACEi = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers II, MCA = mineralocorticoids antagonists, IVA = ivabradine, ARNI = sacubi-trilo/valsartan.
* Compared vs ACEI/ARB + BB.
Modified from: Komajda M et al.[96]

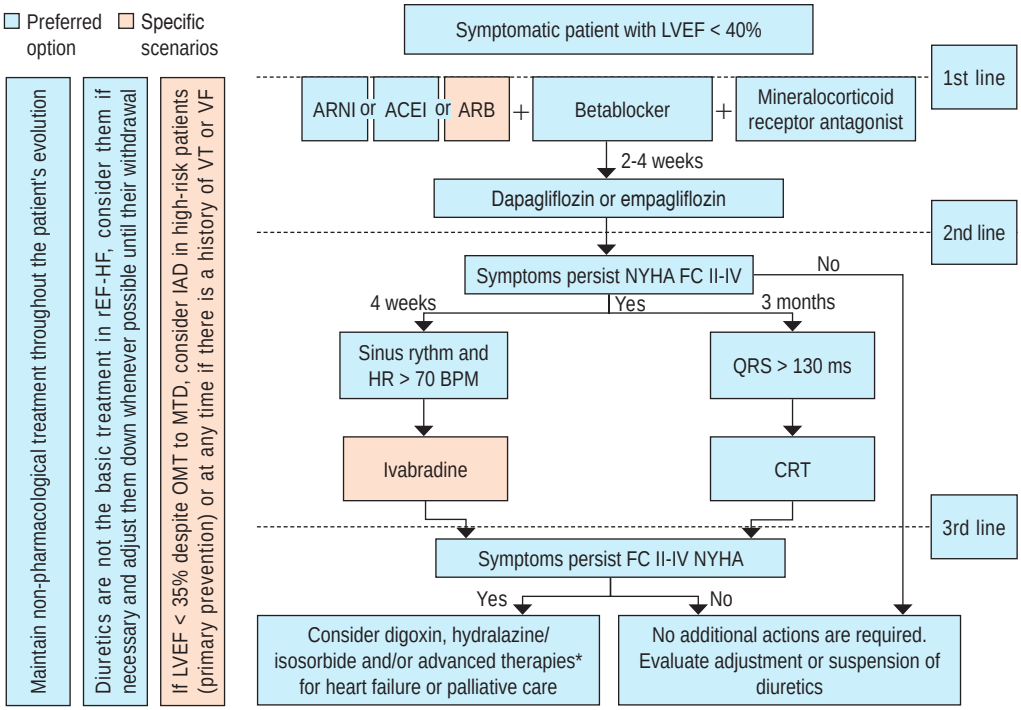


Figure 13:

Heart Failure with reduced ejection fraction General treatment scheme (Non-type 2 diabetic patients).
Abbreviations: ARNI = angiotensin receptor antagonist/neprilysin inhibitor, ACEI = ACE inhibitos, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor agonist, CRT = cardiac resynchronization therapy, DAI = desfibrilador automático implantable, OMT = optimized medical treatment, MTD = maximum tolerated dose, LVEF = left ventricular ejection fraction. * heart failure advanced therapies: cardiac transplantation, mechanical circulatory assist.

c. Any patient in therapeutic optimization protocol, the clinical response, changes in blood pressure, heart rate, and the behavior of biochemical markers, particularly serum electrolytes, creatinine and urea nitrogen levels, should be carefully monitored
d. There are groups of patients who require special evaluation for a therapeutic decision-making *Figure 14*.
e. As long as there is no specific evidence, it is reasonable to apply these therapeutic principles for patients with Heart Failure with Moderately Reduced Ejection Fraction (HF-mrEF)
f. These recommendations are based on current clinical practice guidelines and evidence of new studies with positive results. However, the final decision must be individualized, in accordance with the criteria of the treating medical personnel, and in accordance with current health regulations.

Optimization of pharmacological management and dose titration schemes

Defining the optimal treatment of HF-rEF is not an easy task, particularly at a time when there are multiple therapeutic options whose value is complementary. From this positioning, it was agreed to recognize «**the minimum drug combination needed to remain *symptom-free and/or with improvement of the ejection fraction*» as the optimal medical treatment (OMT)**, as the minimal management to consider therapeutic optimization to triple neuroendocrine control therapy with angiotensin renin system antagonists, beta blockers and mineralocorticoid receptor antagonists; however, for therapeutic optimization in patients who do not achieve symptomatic control with this first step, the incorporation of other alternatives (SGLT2i, ivabradine, digoxin, nitrates/hydralazine) should be considered early according to each patient profile. In this consensus, the term ejection fraction improvement is defined as an increase of 10% of LVEF or more from baseline (in the absence of an episode of exacerbation) or reaching a LVEF > 40% at any time after receiving optimized treatment.

It is important to note that in the field of drug treatment optimization, the quantitative aspect should not be the only one to consider in terms of the number of medicines used.

So reaching the dosages used in clinical trials or those recommended in clinical practice guidelines is a goal to achieve to get the most benefit of this management. It is important to define ***that the maximum tolerated* dose (MTD)** is the one in which patients ***are free of side effects caused by medications*** (mainly symptomatic hypotension). *Table 9* summarizes the recommended doses of drugs used in the management of HF-rEF.

In daily clinical practice it is common for a significant percentage of patients with HF-rEF not to reach the doses recommended by clinical practice guidelines both in the chronic phase of the disease and during the vulnerable period of the disease.[97,98] This is regardless of formal contraindications for its use. The main reasons for not reaching the recommended doses are therapeutic inertia and the presentation of drug side effects, particularly, hypotension.

Reaching the maximun tolerated dose by the patient should always be sought in accordance with the recommendations of clinical practice guidelines or controlled clinical trials.

For this reason, from this consensus it is proposed to use structured schemes for initiation treatment doses and titration in order to increase the number of patients with optimized pharmacological management.

In first scenario, concerning the use of renin angiotensin system antagonists (ACE inhibitors, Angiotensin receptor blockers, Angiotensin receptor blockers/neprilisin inhibitors), it is proposed to take systolic blood pressure as a main variable for dose titration; two main groups are defined, two possible doses, and three moments to reach the maximum tolerated dose in a six week period *Figure 11*; the purpose of this scheme is to limit the risk of severe or symptomatic hypotension with the use of these drugs and at the same time, to promote gradual dose increases up to the maximum tolerated. The dose and group approach is based on the strategies followed in the seminal studies with these drugs.

In second scenario, a scheme for the use of beta blockers (carvedilol, bisoprolol and metoprolol succinate) is proposed, considering two variables (heart rate and systolic blood pressure). As with renin angiotensin system antagonists, two categories are identified according to the evaluation variables, two possible doses and three times from start to the maximum tolerated dose *Figure 12*.

III.3 Cardiac arrhythmias, devices and electrophysiological procedures

Rhythm and conduction disorders are common in HF patients. Among these, Atrial Fibrillation (AF) is the most common arrhythmia. Data derived from various international records show that one third of AF patients can develop HF, and on the other hand, 30-50% of HF patients may have AF.[99] It is therefore concluded that there is a two-way relationship between AF and HF. In patients with established HF, the development of atrial fibrillation complicates the clinical evolution of

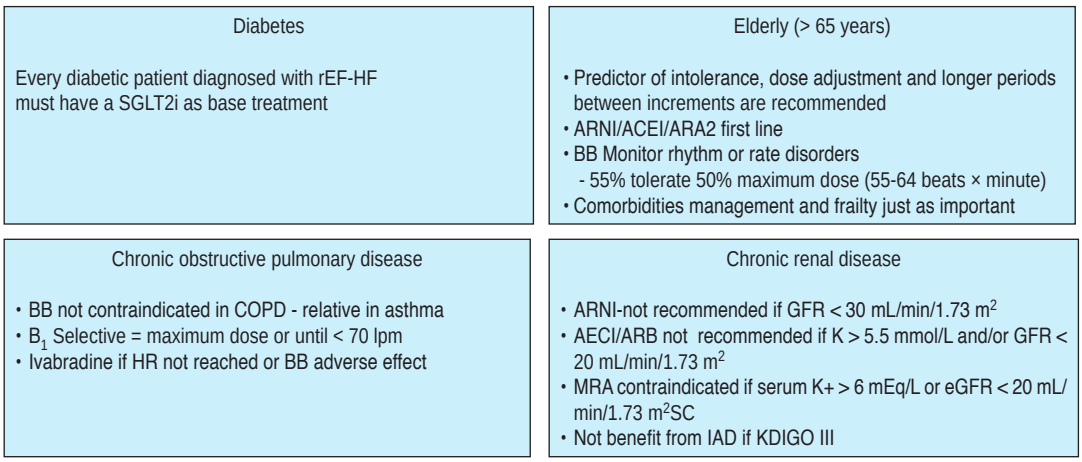


Figure 14:

Pharmacological treatment considerations in special population.

Table 9: Initial and maximum doses of disease-modifying medications for heart failure with reduced ejection fraction treatment (patients without diabetes).

Drug	Initial dose	Maximal dose
ACE inhibitors		
Captopril	6.25 mg every 8 hours	50 mg c/8 hours
Enalapril	2.5 mg c/12 hours	10 mg c/12 hours
Ramipril	2.5 mg c/24 hours	10 mg c/24 hours
Lisinopril	2.5-5.0 mg c/24 hours	20 mg c/24 hours
Sacubitril valsartan	50 mg c/12 hours	200 mg c/12 hours
Betablockers		
Bisoprolol	1.25 mg c/24 hours	10 mg c/24 hours
Carvedilol	3.125 mg c/12 hours	25 mg c/12 hours
Metoprolol succinate	25 mg c/12 hours	100 mg c/12 hours
Angiotensin receptor blockers		
Candesartan	8 mg c/24 hours	32 mg c/24 hours
Losartan	25 mg c/24 hours	50 mg c/12 hours
Valsartan	80 mg c/24 hours	320 mg c/24 hours
Mineralocorticoid antagonists		
Eplerenona	12.5 mg c/24 hours	50 mg c/24 hours
Espironolactona	12.5 mg c/24 hours	50 mg c/24 hours
SGLT2i		
Dapagliflozin	10 mg c/24 hours	
Empagliflozin	10 mg c/24 hours	
Ivabradine	5 mg c/12 hours	7.5 mg c/12 hours

patients, essentially by significantly increasing the risk of thromboembolic complications and on the other hand, AF is in many cases a trigger for episodes of chronic heart failure decompensation.

It is necessary to intentionally explore the presence of atrial fibrillation in every HF patient during their comprehensive evaluation. If identified, therapeutic behaviour should include measures to reduce the risk of thromboembolic events and, as far as possible, to preserve sinus rhythm, if not possible, to achieve heart rate control at least.

In patients with HF and AF with a CHA2DS2-VASC scale 1 score or higher, the use of oral anticoagulation is recommended for the prevention of thromboembolic events.[6,100] Whenever feasible, the use of direct anticoagulants is recommended as the preferred option. This is due to their advantages over ease of use, monitoring and safety.[6]

With regard to heart rate management strategies, evidence indicates that maintaining or restoring sinus rhythm is superior to the heart rate control alone.[101,102] So, antiarrrhythmics are the first line management with amiodarone as the preferred option for patients with HF-rEF; however, its effectiveness in maintaining the sinus rhythm in the medium and long term is debatable. The CASTLE-AF[103] study demonstrated the superiority of transcatheter ablation versus pharmacological treatment in terms of decreased risk of the primary outcome composed of death from all causes/hospitalizations due to heart failure worsening (HR 0.62, 95% CI 0.43-0.87, p = 0.007) in a patients cohort with HF-rEF and paroxystic or persistent atrial fibrillation, recently, the PRECEPT (*Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH SF Catheter Evaluated for Treating Symptomatic PsAF and nonresponse or intolerance to > 1 antiarrhythmic drug (class I or III)*) endorsed the usefulness and safety of transcatheter ablation in persistent atrial fibrillation,[104] although it is true that these patients were not HF carriers, the usefulness of electrophysiological procedures in the contemporary handling of atrial fibrillation was evident. It is therefore suggested that ***whenever possible, transcatheter ablation should be considered as treatment for rhythm control in patients with HF-rEF and paroxysmal or persistent atrial fibrillation.*** In patients where this option is not feasible, pharmacological strategy should continue; however, it is proposed to promote and encourage setting specialized centres for the control and management of cardiac arrhythmias through contemporary electrophysiological procedures of proven usefulness.

In patients with permanent AF where invasive electrophysiological procedures are not feasible, heart rate control strategy should be the option through the use of drugs such as beta blockers, digoxin or their combination.[4,6] In patients who, despite drug treatment, control of the mean ventricular response is not achieved, node ablation and cardiac electrical stimulation may be considered as management through conventional cardiac resynchronization therapy or through hisian stimulation. *Figure 15* summarizes the decision flowchart for the treatment of patients with HF-rEF and permanent atrial fibrillation.

Sudden cardiac death (SCD) is a fatal outcome that often occurs in patients with heart failure, particularly in those with significant impairment of ventricular function (LVEF < 35%). Physiopathological mechanisms involved in this event are multiple and comprise a set of genetic, structural, neuroendocrine expression situations as well as triggers such as myocardial ischemia, QTc prolongation, electrolytic disorders among others as outlined in *Figure 16*.[105] Optimal pharmacological management has shown to have a beneficial impact on reducing the risk of cardiovascular death from both CF progression and sudden death,[106] even post hoc analyses of the PARADIGM-HF study demonstrated an early and beneficial effect of sacubitril/valsartan compared to enalapril to reduce the risk of CSD,[107] which is why clinical practice guidelines recommend the use of Sacubitril/valsartan in conjunction with beta blockers and antialdosteronic agents to reduce the risk of SCD in patients with HF-FEr and ventricular arrhythmias.[4] However, in spite of these benefits, there is a significant residual risk of SCD in patients who are still receiving optimized drug treatment, this risk is increased in those patients surviving an episode of SD. Implantable cardioverter defibrillators (ICDs) are intracardiac electronic devices that have proven to be a useful option for the treatment of potentially lethal arrhythmias in patients with HF-rEF who despite receiving optimal medical treatment (OMT) persist at high risk of SCD. Contemporary clinical studies have been compelling in pointing out the usefulness of these devices and that is why clinical practice guidelines recommend them for both primary and secondary prevention of a SCD.[4] ***It is recommended to implantable cardioverter defibrillators (ICDs) in patients with HF-rEF who despite having optimal medical treatment (OMT) at maximum tolerated doses (MTDs) persist with a LVEF < 35%, to decrease the risk of death due to ventricular arrhythmias.*** The term high risk is introduced to define patients with ischemic etiology or those with non-ischemic causes under 60 years of age. In patients with a history of ventricular tachycardia and/or ventricular fibrillation, these devices should be implanted as secondary prevention. *Figure 17* outlines the indications for the implantation of ICDs in patients with HF-rEF. It is important to emphasize that for patients in primary prevention group, OMT must last at least three months before implant decision because of recent evidence of OMT benefits on SCD development. Similarly, patients must have a life expectancy of one year or more, so that patients with end-stage malignancies, or those with a life expectancy limitation condition would not be suitable candidates for IDs implantation. In patients surviving a myocardial infarction, who are potential candidates for implantation of an ICD, at least 40 days after the acute event should be waited to recognize and treat potentially reversible causes of CSD.[4] It is essential to note that ***the decision to implant an ICD must be made in consensus and the procedure should be reserved to experts in electrophysiology***

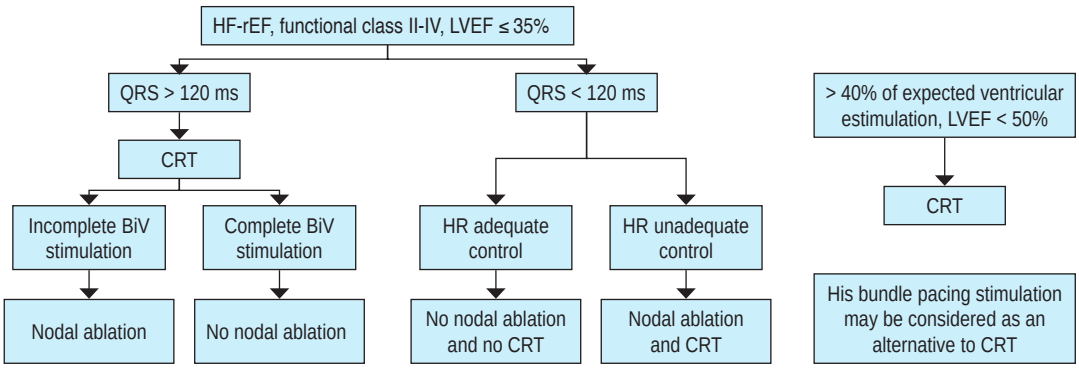


Figure 15: Management of permanent atrial fibrillation: drug treatment, node ablation and cardiac resynchronization therapy.
HF = heart failure, FC = functional class, LVEF = left ventricular ejection fraction, BIV = biventricular, CRT = cardiac resynchronization therapy, HR = heart rate.

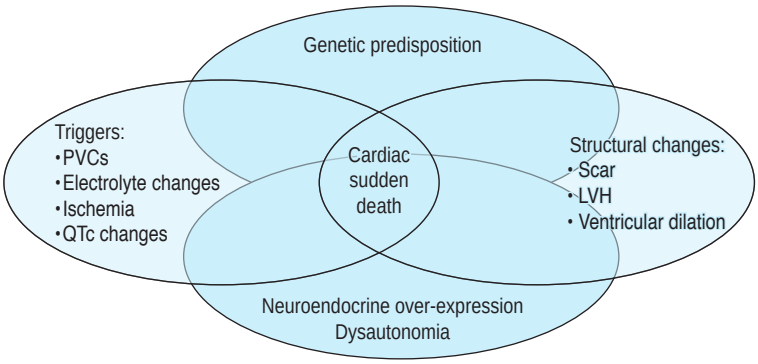


Figure 16: Proposed mechanisms for the occurrence of sudden heart failure death.
doi: http://dx.doi.org/10.1016/j.hrthm.2017.09.025

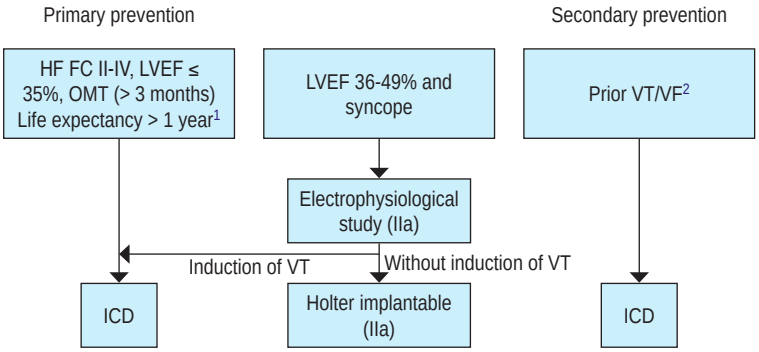


Figure 17: Indications for implantable cardioverter defibrillators.
[1] > 60 years and non-ischemic cardiomyopathy, assess benefit (DANISH).
[2] > 40 days post-infarction, without reversible causes.
ICD = implantable cardioverter defibrillators.

in order to increase the potential for success in the implant and reduce risks of associated complications.

In addition to the population strictly classified as candidates for the use of ICDs in primary prevention, there are populations that require special consideration, either because they have medical indication to be an ICD carrier, and belong to a subgroup where the benefit is debatable, or because they do not have the conventional medical indication, and yet have an increased risk of sudden death.

We will initially refer to those who meet the criteria for having an ICD in primary prevention, but the benefit in mortality is less than expected, this applies to people > 70 years and to patients with stage V chronic renal failure (CRF) (with and without dialysis). Cardiovascular disease is directly related to age, so the older a person is the more likely to have systolic dysfunction of any cause, along with a higher likelihood of having an indication for an ICD in primary prevention, however, while appropriate therapies for ICDs are similar across the entire age spectrum, mortality will continue to be higher as from the age of 70,[108,109] this phenomenon was explained very precisely in a subgroup analysis of the DANISH study, where the potential benefit of ICDs depended on the risk of sudden death in relation to the risk of non-sudden death,[110] so the decision to implant such a device should include all the individual comorbidities that may predispose to death despite a defibrillator. The population with stage 5 CKD represents a challenge at the time of decision-making, since in stages 3-5 the reduction in the estimated glomerular filtration rate progressively increases the risk of sudden death and is estimated to correspond to approximately 26% of all deaths.[111,112] Unfortunately, there is evidence in the population without heart failure where sudden death was related to non-defibrillable bradyarrhythmias or ventricular arrhythmias and the evidence that exists in patients with advanced stage CKD and heart failure comes from meta-analysis and cohort studies none demonstrating a clear benefit in the use of ICDs in primary prevention, so your prescription should be discussed individually with the entire multidisciplinary team.[113-116]

Finally, the population with mild-moderate LVEF dysfunction (> 35%) and syncope episodes, an electrophysiological study for induction of ventricular arrhythmias is recommended, if positive an ICD should be implanted, and if negative, the possibility of an arrhythmic origin for the syncope is uncommon.[117] However, depending on the suspicion degree it is desirable to consider implanting a long-lasting heart monitor. In recent years, promising information has been generated regarding the usefulness of various cardiac magnetic resonance techniques to assess heterogeneity, location and extent of fibrosis as a marker of sudden cardiac death,[118,119] at the moment its widespread use is not recommended for decision-making in isolation until there are clinical trials available, currently the CMR GUIDE (Cardiovascular

magnetic *resonance-Guided management of mild left ventricular systolic dysfunction)* study is currently under development assessing the ICD implant in primary prevention for patients with late gadolinium enhancement CMR with LVEF 36-50%.[120]

While the defibrillator significantly reduces sudden deaths, patients with recurrent ventricular tachycardia despite OMT and antiarrrhythmic management with amiodarone should be considered for catheter ablation rather than escalation of antiarrrhythmic treatment. This is based on recent evidence in which the invasive strategy reduced the death risk rate, recurrence of ventricular tachycardia or ICD discharges by up to 28%.[121] *Figure 18* establishes the proposed decision flow for the management of recurrent ventricular tachycardia.

Ventricular dyssynchrony is common in heart failure patients. From a conceptual point of view this phenomenon is the product of structural and functional abnormalities that affect the normal sequence of heart electromechanical activation and consequently alterations occur in all phases of the cardiac cycle resulting in a decrease in heart mechanical efficiency as well as an increase in the hemodynamic overload resulting in a greater neuroendocrine over-expression, thus closing a vicious cycle that aggravates disease and overshadows its prognosis.[122-124]

Cardiac resynchronization therapy (CRT) is a modality of cardiac electrical stimulation in which multisite stimulation at the atrial and biventricular level aims to recover the normal cardiac electrical activation sequence and consequently improve heart contractility and electromechanical efficiency.

CRT usually stimulates three specific sites: right atrium (RA), right ventricle (RV), and left ventricle (LV) through the coronary sinus; however in recent years, Hisian stimulation provides a new alternative for ventricular stimulation.

The original clinical trials (COMPANION, CARE-HF, RAFT, MADIT-CRT and REVERSE)[125,126] have been consistent in demonstrating the efficacy and safety of this therapy in improving the functional class and delaying heart failure progression. For this reason, CRT is recommended by all contemporary clinical practice guidelines to optimize the management of heart failure with reduced ejection fraction with evidence of dyssynchrony.[4]

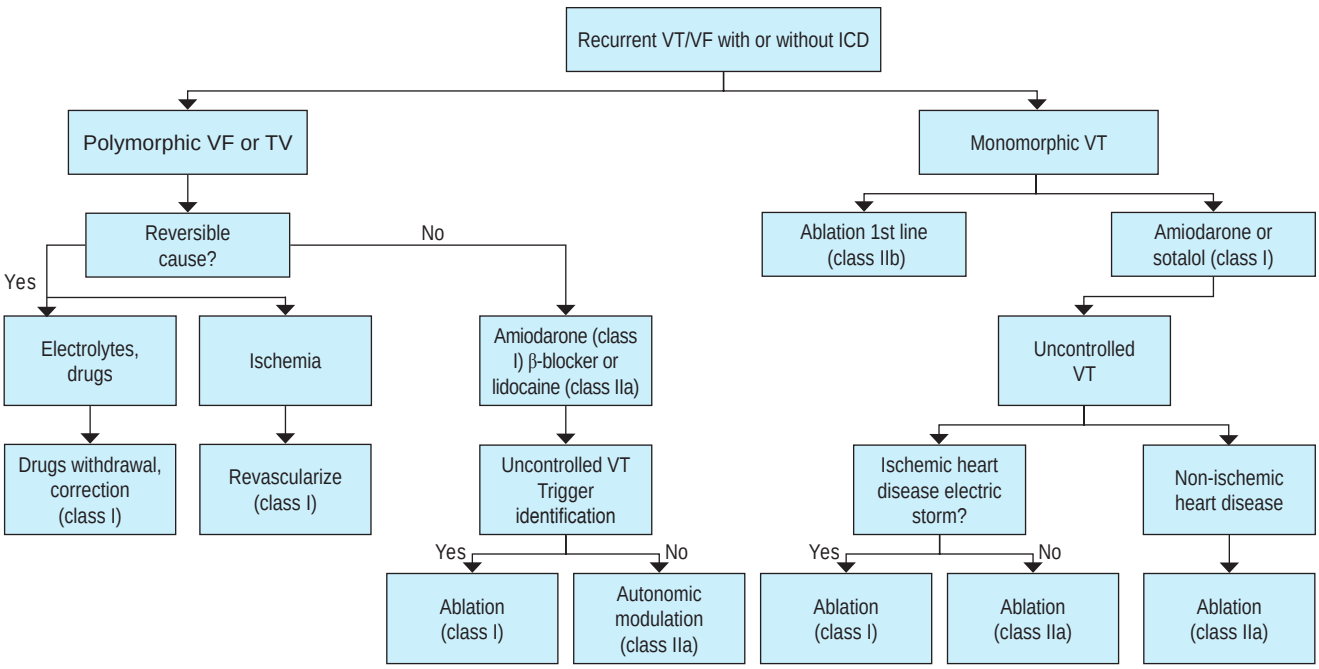


Figure 18: Management of recurrent ventricular tachycardia. VT = ventricular tachycardia, VF = ventricular fibrillation, ICD = implantable cardioverter defibrillators.

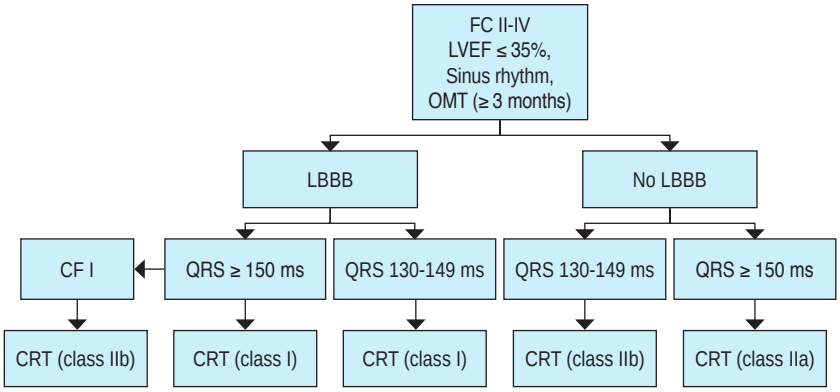


Figure 19:

Selection criteria for implantation of cardiac resynchronization therapy. LBBB = left bundle branch block, OMT = optimal medical treatment, CRT = cardiac resynchronization therapy FC II-IV.

From a point of view of the operational definition of the TRC effects are considered responders to patients who after a six months follow-up or more, present improvement of functional class (decrease of one degree or more of the NYHA functional class) and an increase of 5% or more of the LVEF compared to baseline measurement.[127] «*Super responders*» are considered to be those who manage to remain as NYHA Functional Class I with an increase of 20% or more of the LVEF from baseline or reaching a LVEF of 50% or more at the end of follow-up.[128] On the other hand, patients who show no clinical or echocardiographic improvement or those suffering progressive impairment that leads to transplantation or death are considered non-responders.[129]

From this positioning, we issue the following recommendations regarding cardiac resynchronization therapy:

- **Cardiac resynchronization therapy should be indicated early in all patients with symptomatic HF-rEF whose QRS width is equal to or larger than 130 msec in presence of left bundle branch blocking or QRS width of 150 msec or more in patients without left bundle branch blockage.**
- **The candidates for CRT must and receive OMT to MTD at least three months prior to implantation.**
- **Echocardiography or cardiac magnetic resonance imaging is useful for the study of ventricular dyssynchrony, monitoring and optimization of CRT but they are not a criterion for implant selection.**
- **The implantation of devices for CRT should be carried by experts in electrophysiology.**
- **The implant decision, optimization and follow-up should be done in agreement with clinical cardiology (preferably within a structured heart failure program).**
- **Cardiac resynchronization therapy is not a substitute for drug treatment, it complements it.**
- **In all CRT patients, attempts should be made to maximize doses of neuroendocrine control drugs and should not be discontinued despite evidence of response to this therapy.**

Figure 13 outlines the place of CRT within the therapeutic algorithm in HF-rEF *and Figure 19* the flow according to the type of blockage in the EKG.

In order to increase the number of patients responding to CRT, three moments should be considered:

1. **Patient selection.** The most important criteria for selecting CRT candidates lies in the widening of the QRS complex on the 12-lead electrocardiogram at rest. Evidence of improvement in CRT in patients with normal QRS is controversial mainly from the results of the ECHO-CRT[130] study where patients with QRS of 120 msec or less not only did not demonstrate improvement after receiving CRT, but increased adverse outcomes including cardiovascular death. Therefore, this therapy should be restricted to those patients with QRS of 130 msec or rather be discussed for certain patients with

HF-rEF who necessarily require permanent cardiac electrical stimulation. However, it is well known that the single width of the QRS should not be considered as an a priori criterion of good response, so in addition to this variable, the morphology of the QRS should be considered. Patients with true Complete Left Bundle Branch Block morphology are the group of candidates most likely to respond favorably. So we should be especially careful when interpreting an EKG while searching FLHBBB.[131] In patients without this morphology, a QRS of 150 msec or more should be estimated. Other a priori criteria of good response to CRT is female gender, non-ischemic etiology of heart failure, and dyssynchrony proven by imaging (not a selection criteria). In contrast, male patients, those with ischemic etiology or evidence of large fibrosis areas are the ones who have shown the lowest favorable response rate so in such cases and particularly if the resource is limited, their adequacy for CRT implantation should be carefully re-evaluated. *Figure 20* summarizes the variables to consider in the selection of the best candidates to receive CRT.

2. **Implant.** As noted above, under suitable conditions, the implantation of CRT devices should be consider by specialists in electrophysiology with specific training. This is because improper placement of stimulation electrodes (particularly in coronary sinus) or Hisian stimulation is definitive to ensure a therapeutic response. In addition, limiting the implant to specialized groups decreases the number of complications around the procedure.
3. **Follow up.** Patient follow-up should be performed with clinical cardiologists, heart failure specialists (when possible) and Electrophysiologists under a multidisciplinary approach that allows not only to adjust the nominal devices parameters to the particular requirements of each case, but also that patients may receive the greatest benefit from non-pharmacological and pharmacological treatment once they have taken to CRT. Therefore, patients who have received CRT should not abandon structured follow-up under any circumstances.
   In cases of atrial fibrillation, CRT remains a controversial topic;[132] however, in patients that are being considered for CRT despite the evidence of AF, the decision should be made collectively by a multi-disciplinary medical team considering all potential risks and benefits of such intervention. Therefore, it is suggested that at no time, this decision should be made by a single person.

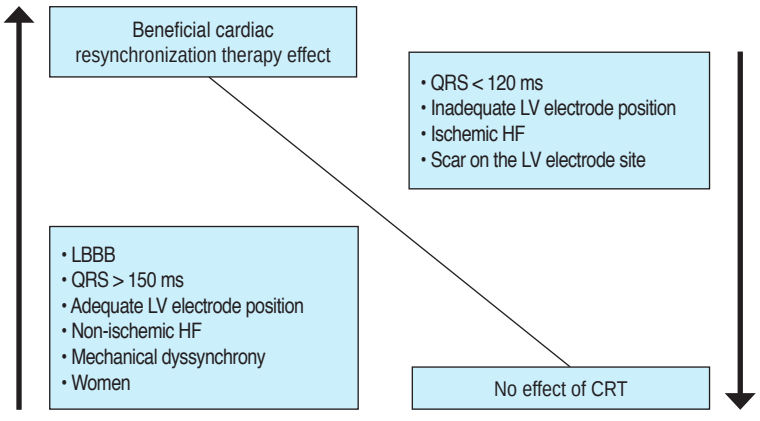


Figure 20: A priori assessment of cardiac resynchronization therapy response. LBBB = left bundle branch block, QRS. LV = left ventricle, HF = heart failure, CRT = cardiac resynchronization therapy.

III.4 Managing comorbidities in Heart Failure

HF is a heart disease with multiorgan involving. There are several morbid conditions that co-exist in patients with HF and have a very significant role in HF natural history. ***A comprehensive approach to heart failure should undoubtedly consider comorbidities and their management***.

According to international records, most common comorbidities in HF are high blood pressure, Diabetes mellitus, Iron deficiency with or without anemia, nephropathy, atrial fibrillation and in case of Mexico, obesity. There are other conditions such as sleep apnea-hypopnea syndrome (obstructive or central), neuropsychiatric disorders such as depression and dysthymia among others.[133] Due to its frequency in Mexican population and the scope of this document, the aspects related to high blood pressure, diabetes mellitus, iron deficiency, obesity and nephropathy will be described.

1. High blood pressure management in heart failure

Arterial Hypertension is the most common chronic degenerative disease in Mexico. It is estimated that there are more than 20 million patients with High Blood Pressure nowadays. It has also been recognized as a heart failure cause. Timely treatment of arterial hypertension is essential to reduce the risk of progression to Heart Failure.[134,135] From this positioning it is suggested that ***in every patient with high blood pressure, current recommendations of clinical practice guidelines on Arterial Hypertension should be followed in order to decrease progression to HF***. In patients with hypertensive HF-rEF, achieving therapeutic goals is a priority, and it should be remembered that most drugs used for HF neuroendocrine control (ACEIs, ARBs, RNAIs, beta blockers, antialdosteronics, diuretics) have an effect on blood pressure, so in daily practice it is common for HF base treatment to also impact on blood pressure. In those patients with HF-rEF in whom, despite triple neuroendocrine control therapy and the use of diuretics at recommended doses, blood pressure control target is not achieved, the use of drugs such as dihydropiridin calcium antagonists or a combination of nitrates with hydrarazine as discussed in this document may be considered.[4,136] It should be noted that the use of calcium antagonists such as verapamil or diltiazem are contraindicated by their negative inotropic effect and the risk of heart failure worsening. In case of heart failure with preserved ejection fraction, blood pressure values control is a first-rate measure (see relevant section); however, due to hemodynamic behavior of these patients, it should be noted that care should be extreme close with the use of diuretics, since these drugs have a narrow therapeutic range in this group of patients.[137]

2. Diabetes treatment in heart failure

Diabetes mellitus should be considered as cause and effect of HF. Type 2 diabetes patients are known to have a double risk of developing HF during their natural history,[138] on the other hand, patients with HF and Diabetes have a worse prognosis in terms of morbi-mortality.[139] These data have been supported by recent evidence in clinical trials where patients with HF-rEF who are disglycaemic or who live with Diabetes have a more unfavorable clinical evolution than HF patients with normal glucose.[140] Mechanisms involved in the development of HF in patients with diabetes are multiple and include atherosclerosis plaques formation resulting from diabetes and other vascular risk factors that are capable of conditioning ischemic heart disease; however, there are mechanisms not linked to atherosclerosis such as autonomic dysfunction, overactivation of the autonomic nervous system, resistance to natriuretic peptide system, direct glucotoxicity to cardiomyocytes and cardiac bioenergy alterations.[141-143] In fact, diabetic cardiomyopathy is fully accepted as a form of heart failure in the absence of coronary heart disease.

Therefore, from this positioning it is recommended ***to intentionally look for the presence of diabetes or dysglycemia in the approach for HF patients.***

Hence, there are two relevant aspects to be treated: reduction risk of HF in patients with Diabetes, and treatment of Diabetes in patients with HF.

For the first case, we should emphasize that Diabetes mellitus management has been enriched in recent years, which focused on blood glucose control to the prevention of metabolic, renal, and cardiovascular events in the present. Usefulness profile of each of the glucose-lowering agents should be defined, not only considering its effect on the achievement of fasting blood glucose or glycosylated Hemoglobin goals but also on the reduction of outcomes such as HF. *Table 10* summarizes characteristics of drugs used for DM2 management and their potential effects on HF development. According to the most relevant Clinical Practice Guidelines, in patients with T2DM and high risk for developing HF, there are two pharmacological groups that have shown the greatest benefit in association with metformin or even as a first-line management, these are the sodium-glucose contransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1a).[144-147] ***In the specific field of diabetes in HF, SGLT2i (empagliflozin, canagliflozin, dapagliflozin)***

should be considered as preferred option. This is because the evidence from original studies has been robust and unique in noting that these drugs reduce the risk of developing or worsening HF in T2DM patients[78-80] *(Table 11)*. In patients who are intolerant or have a contraindication for the use of a SGLT2i, or who do not achieve metabolic control despite the combination of a SGLT2i and metformin, GLP1as with demonstrated cardiovascular benefit are the option to choose.[144,145,147] If it is decided to use a SGLT2i in type 2 diabetic patients, it

Table 10: Pharmacological treatment for type 2 diabetes.

Drug	Efficacy (glucose control)	CV effects (high-risk patients or patients with overt CV disease)	CV effects (heart failure patients)	Risk of hypoglycemia
Biguanides	Intermediate	Insufficient information	Insufficient information	Yes
Metformin	High	Potentially beneficial	Neutral	No
Insulins	Very high	Neutral	Neutral	Yes
DPP4 Inhibitors (DPPi-4)	Intermediate	Neutral	Potential risk (Saxagliptin)	No
Thiazolidinediones (glitazones)	Intermediate	Potentially risky (Pioglitazone)	Risk increase	No
GLP1 agonists (GLP-1a)	High	Neutral with potential benefit	Neutral	No
SGLT2 inhibitors (SGLT2i)	Intermediate	Beneficial	Protector	No

Cigarroa LJ et al.[15]

Table 11: Role of SGLT2 inhibitors in the prevention of heart failure in type 2 diabetes.

	EMPA-REG OUTCOME	CANVAS Program	DECLARE TIMI 58	CREDENCE
Drug	Empagliflozin 10 o 25 mg	Canagliflozin 100 o 300 mg	Dapagliflozina 10 mg	Canagliflozina 100 mg
Patients (n)	7,020	10,142	17,160	4,401
Hb1Ac (%)	8.1	8.2	8.3	8.3
Type 2 diabetes (%)	100	100	100	100
eGFR (mL/min/1.73m^2 SC)	74	77	85	56 (included patients between 30-90 mL/min (1.73m^{2}SC)
Previous CV disease (%)	100	66	41	50
Follow-up (years)	3.1	2.4	4.2	2.62
MACE	0.86 (0.57-0.82)	0.86 (0.75-0.97)	0.93 (0.84-1.03)	0.83 (0.68-1.02)
Death by any cause	0.65 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.83 (0.68-1.02)
Cardiovascular death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.61-1.00)
Heart failure hospitalization	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47-0.80)
Renal outcomes	NA	0.60 (0.47-0.77)	0.76 (0.67-0.87)	0.70 (0.59-0.83)

NA = Not available.
Cigarroa LJ et al.[15]

Tabla 12: Practical recommendations for the safety use of SGLT2i in patients with heart failure and type 2 diabetes.

Contraindications	Precautions	Start up in clinically stable ambulatory patients (c/24 hours)	Additional comments
• Decompensated heart failure • State of shock • TFGe < 25 mL/min/1.73 m^2SC • Allergy or intolerance to SGLT2i • Diabetic ketoacidosis • Severe peripheral arterial disease with high risk of amputation • Active genitourinary infection	• History of genitourinary infections • Risk of volume depletion (it is suggested to adjust the dose of diuretics before starting an iSGLT2) • Low blood pressure • Hypoglycemia history	• Empagliflozin 10 mg • Dapagliflozin 10 mg • Canagliflozin 100 mg	Required monitoring of • Serum glucose • Hb1Ac • Blood pressure • Weight • Serum Cr, eGFR • Signs of genitourinary infection In case of not reaching the Hb1Ac goal: • Incorporate other medications according to the recommendations of the clinical practice guidelines

eGFR = estimated glomerular filtration rate, Hb1Ac = glycosylated hemoglobin, Cr= creatinine.

is important to note that caution should be exercised to avoid volume depletion, to this end, diuretic doses should be adjusted if the patient uses them. Similarly, its use should be defered in patients at high risk of diabetic ketoacidosis (DKA), *(Table 12)* summarizes practical advices for the safe use of SGLT2i in patients with HF.

In patients with HF and diabetes mellitus, it is important to ensure metabolic control. Some aspects should be consider such as the risk of hypoglycaemia, the duration of diabetes and estimated life expectancy. In patients at high risk of hypoglycaemia, with long lasting diabetes or where long-term life expectancy is limited it is suggested that a reasonable therapeutic target in terms of Hb1Ac be around 7% and not less than 6%.[143,145] Based on recent scientific evidence, it is proposed that ***in patients with HF-rEF and DM2, SGLT2i should be considered as initial therapy along with a neuroendocrine control therapy*** *(Figure 21)*. This is due to the beneficial effects on metabolic control, and cardiovascular and renal protection of this pharmacological group.

Metformin can be used in combination with a SGLT2i to achieve Hb1Ac goals, and if blood glucose control is not achieved despite a dual therapy, a third option, as a GLP1 agonist with proven cardiovascular safety may be added. In case metabolic control is not achieved despite oral combination therapy, the use of insulins is an option; however, this decision should be made cautiously and preferably in conjunction with specialists in the field (endocrinology or internal medicine).

3. Addressing and managing iron deficiency

Iron deficiency (ID) with or without anemia is a common condition in patients with heart failure. It is estimated that in chronic outpatients, may be present in up to 50% of cases and in acute heart failure up to 80%.[148-151] In multiple studies ***iron deficiency has been associated with a poor HF evolution, so it should be considered as a prognostic factor.***

From a pathophysiological point of view, ID is able to produce mitochondrial dysfunction, alterations of cardiac bioenergy, inadequate ventricular remodeling, decreased contractile efficiency and increased apoptotic activity of cardiomyocytes, which clinically results in impaired functional capacity and increased morbidity in patients with HF *(Figure 22)*.

Within the causes of ID in HF we find a decrease in intestinal absorption of Fe^{++}, inhibition of the type 1 transferrin receptor, alterations of hepcidine metabolism and an increased iron losses.[151]

Therefore, ***in the comprehensive approach of all patients with HF, iron deficiency should be intentionally sought,*** particularly in those with Hb < 14 g/dL.

From a practical point of view, iron kinetics is a simple and accessible study to know the status of patients regarding the presence of ID. Following the operational definition of the current Clinical Practice Guidelines,[4] a HF patient is considered to have ID when:

1. Serum ferritin is less than 100 µg/L
or
2. Serum ferritin is between 100-299 µg/L and transferrin saturation is less than 20%.

In case patients whose meet these criteria, parenteral iron supplementation is a therapeutic alternative that has been shown to be effective in improving functional class and functional capacity as well as hard outcomes such as decreased hospitalizations and mortality.[152,153]

It should be noted that the use of ***iron should be administered parenterally (endovenous) and as ferric carboxymaltose formulation*** as demonstrated by clinical trials. Oral Iron supplementation has not demonstrated benefits, and the use of perenteral iron dextran is not recommended due to adverse events, particularly the risk of anaphylaxis.

Figure 23 summarizes the protocol for patient selection and parenteral iron administration in HF patients.

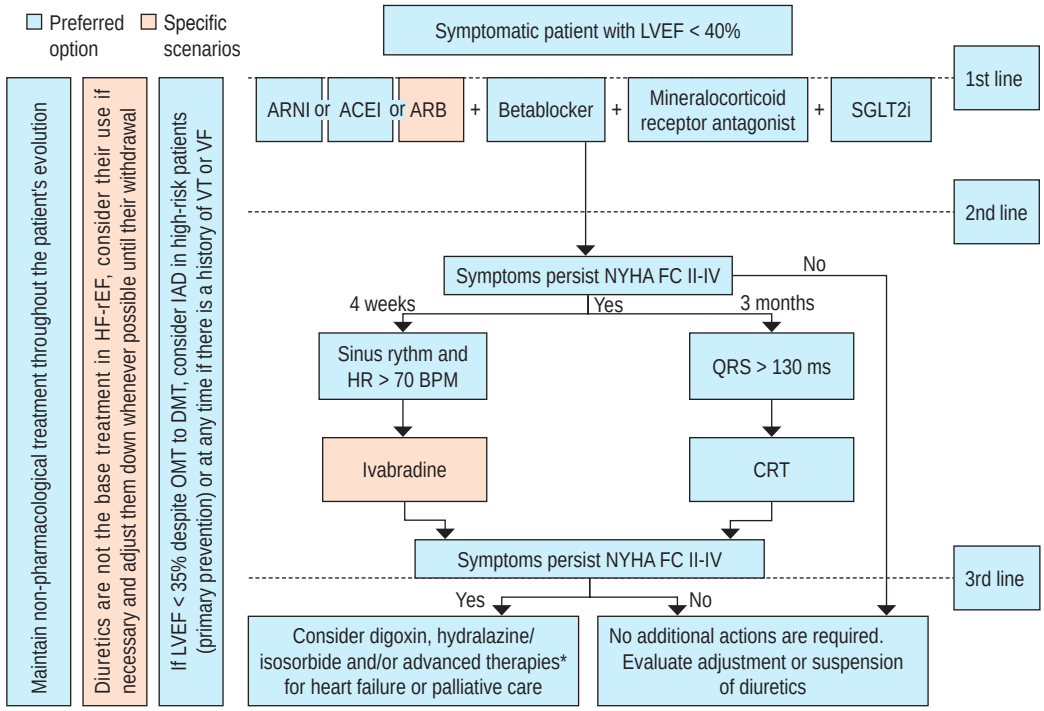
Evidence of chronic use of parenteral iron in heart failure is insufficient, so at this time it is not recommended as part of the base management of patients with ID-free HF or in whom this abnormality has been corrected.

4. Obesity and heart failure

In Mexico, obesity and overweight are a public health problem due to their high prevalence as well as the impact of obesity on diseases such as diabetes, hypertension or dyslipidemias. In the case of Heart Failure, obesity has been associated with the development of HF with preserved ejection fraction; however, the impact on the genesis of HF with reduced LVEF remains controversial.[154]

Figure 21:

Heart failure with reduced ejection fraction general treatment scheme (patients WITH type 2 diabetes). ARNI = angiotensin receptor antagonist/neprilysin inhibitor, AECI = ACE inhibitors, ARB = angiotensin receptor blocker,MRA=mineralocorticoid receptor agonist, CRT = cardiac resynchonization therapy, IAD = implantable automatic defibrilator, OMT = optimized medical treatment, MTD = maximum tolerated dose; LVEF = left ventricular ejection fraction. * Heart failure advanced therapies: cardiac transplantation, mechanical circulatory assist.



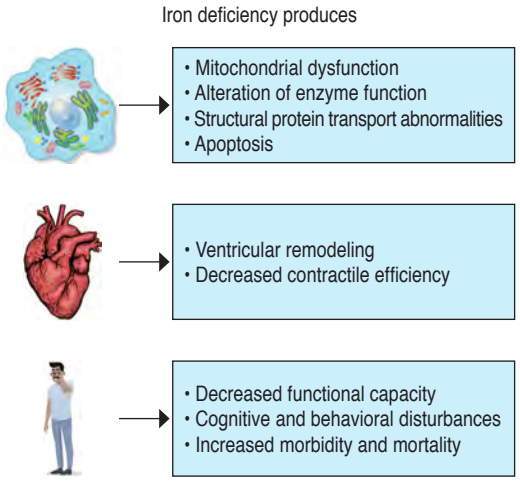


Figure 22: Pathophysiological consequences of iron deficiency Iron deficiency produces.

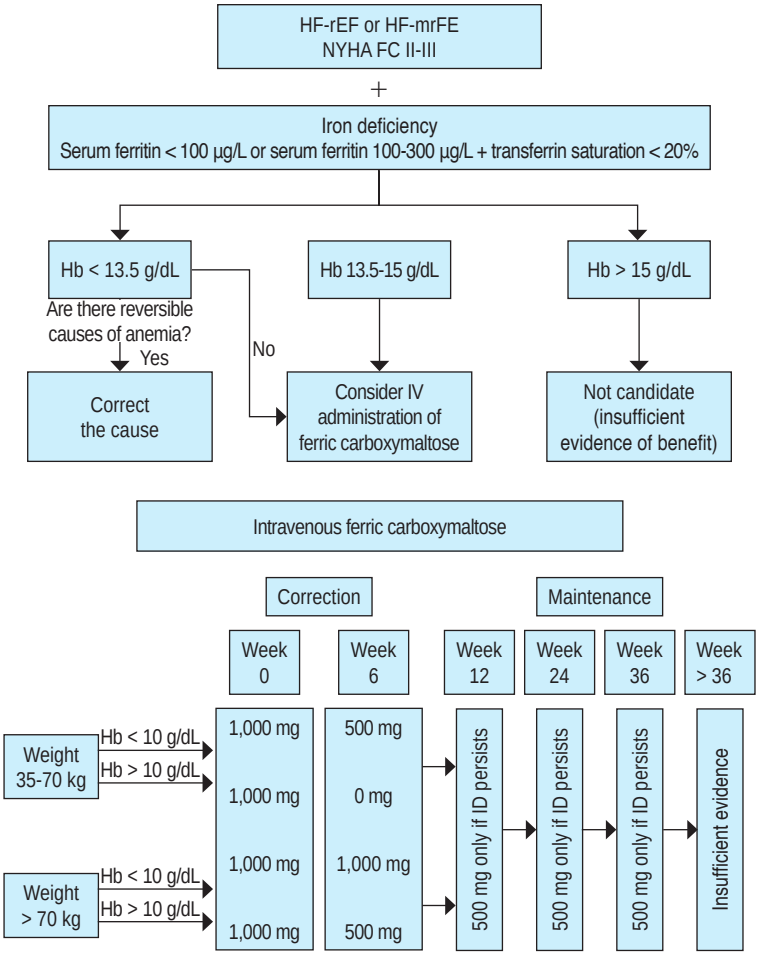


Figure 23: Practical use of parenteral iron in non-acute chronic heart failure. Modified from: Rocha et al.[149]

There are several pathophysiological pathways that converge both in obesity and heart failure, which are neuroendocrine overactivation, endothelial dysfunction, inflammation and increased oxidative stress, among others. These phenomena are associated with microvascular dysfunction, increased vascular stiffness and, at the cardiomyocyte level, alterations in intracellular calcium coupling, dysfunction in titin phosphorylation, cardiomyocyte hypertrophy, and diastolic dysfunction.[154,155]

While the effects of weight loss through procedures such as bariatric surgery have shown improvement in various hemodynamic parameters such as pulmonary capillary pressure, right atrium pressure and pulmonary blood pressure,[156] these results have not resulted in a decrease of major cardiovascular events, so these procedures are not recommended as routine management of heart failure.

Therefore, ***evidence regarding the management of obesity in HF is controversial;*** in fact, the term «obesity paradox in HF»[154,157] has been coined, since observational studies have shown that patients with HF-rEF and obesity or overweight may have a better evolution than those with malnutrition or cachexia. Therefore, ***non-pharmacological measures should be intensified in the management of HF and obesity to keep patients in numbers close to the ideal weight in order to improve symptoms and the metabolic profile;*** however, the use of invasive weight reduction techniques is not recommended as a routine measure and should only be considered in patients with morbid obesity and in consensus with a multidisciplinary group.

5. Managing kidney disease and heart failure

HF and chronic kidney disease are entities that often co-exist and overshadow the prognosis of patients with HF. In acute heart failure it is estimated that up to 64% of patients may show some degree of renal dysfunction and in patients with Chronic Heart Failure the prevalence is around 30%.[158,159]

From a pathophysiological point of view, it can be supported that patients with renal impairment may develop heart failure, while patients with heart failure are a source of renal dysfunction creating a vicious cycle.[160,161]

Mechanisms involved include neurohumoral over-expression, increased central venous pressure, low cardiac output, increased oxidative stress, increased apoptosis (cardiac and renal), the coexistence of morbid factors (i.e. diabetes) and even nephrotoxic effects of polypharmacy.

Conceptually, this binomial has been defined as cardiorenal syndrome and there are 5 different types *(Table 13)*.[162] For the scope of this document, type 1 cardiorenal syndrome (see management section of Acute Heart Failure), and type 2 cardiorenal syndrome will be addressed.

For type 2 cardiorenal syndrome. From this positioning the following arises:

a. **In any patient with heart failure, renal function should be assessed and monitored.**
b. **Biochemical markers are a useful tool for a basic and advanced evaluation of kidney function. Mainly serum creatinine and albuminuria tests as routine examinations for every patient. In special cases, the type 1 renal damage molecule (KIM-1), IL-18, and advanced protein glycation products (AGEs) are biomarkers that allow a thorough study of renal involvement.**
c. **For the calculation of the estimated glomerular filtration rate (eGFR) the use of the CKD-EPI formula is preferred.**
d. **Imaging studies such as Doppler ultrasound are indicated in every patient with Chronic Heart Failure and evidence of kidney dysfunction and damage.**
e. **The use of diuretics should be rationalized to prevent volume depletion and neuroendocrine over-activity.**
f. **The use of angiotensin renin system antagonists is critical to improve clinical course of HF and also to prevent the development of type 2 cardiorenal syndrome.**
g. **The use of SGLT2i in patients with HF and diabetes is a measure that has shown cardiovascular and renal benefits, so it should be considered as the preferred option for managing diabetes in HF.**
h. **In non-diabetic patients, in HF-rEF therapeutic optimization protocols the use of SGLT2i added to neuroendocrine control drugs, is an alternative to decrease cardiovascular and renal outcomes, so they should be considered early.**
i. **Blood potassium levels should be monitored and if hyperkalemia is detected adjust the doses of the RAAS antagonists, and medicines that may cause or aggravate hyperkalemia.**
j. **In patients responding to cardiac resynchronization therapy there may be additional benefits in terms of improved renal function. This effect is explained by**

Table 13: Cardiorenal syndrome classification.

Types	Classification	Characteristics	Comments
1	Acute cardiorenal	The acute cardiac failure conditions an acute renal failure	Cardiogenic shock, decompensated chronic heart failure
2	Cardiorenal chronic	Chronic cardiac dysfunction produces chronic impairment of kidney function	Chronic cardiac failure
3	Acute reno-cardiac	Acute renal failure leads to acute heart failure	The acute hemodynamic overload of acute renal failure in conjunction with inflamatory and metabolic alterations lead to an acute cardiac failure
4	Chronic reno-cardiac	Chronic renal disease produces cardiovascular dysfunction including heart failure	In chronic renal failure there may be cardiac remodeling and heart failure (cardiomyopathy associated with chronic kidney disease)
5	Secondary cardiorenal syndrome	A systemic disease conditions renal and heart failure	Diabetes, amyloidosis, sepsis

improved renal perfusion and decreased venous congestion. Therefore, this therapy should be considered early in the candidate population.

k. **Polypharmacy should be tested and doses and combinations of medicinal products with nephrotoxic potential adjusted.**
l. **The use of futile medication or drugs with a potential risk of nephrotoxicity should be avoided.**
m. **Whenever possible, a multidisciplinary approach between cardiology and nephrology should be carried out for the management of type 2 cardiorenal syndrome.**
n. **It is important to request the availability of drugs for the management of hyperkalemia in Heart Failure, such as Patiromer.**

III.5 Invasive management of heart failure

In certain specific scenarios, cardiovascular surgery and interventional cardiology offer therapeutic options of undeniable value for the integral management of Heart Failure, among these alternatives highlight:

1. Myocardial revascularization (surgical or interventional)

Ischemic heart disease is one of the most common chronic heart failure causes. Paradoxically, scientific evidence regarding the value of revascularization procedures in modifying the prognosis of the disease is limited. There are even studies with controversial results regarding the usefulness of myocardial feasibility studies as an assessment parameter for the revascularization effect in patients with HF.

Existing Clinical Practice Guidelines consider myocardial revascularization procedures for angina relief in patients with heart failure who persist symptomatic despite treatment with antianginal drugs.[4,163]

In original studies such as STICH Trial,[164] it was demonstrated that myocardial revascularization surgery in patients with heart failure with LVEF less than or equal to 35% with evidence of proximal anterior descending coronary artery disease (LAD) (not left main coronary artery) or multivessel disease in whom more than 10% of myocardium is dysfunctional but viable, could benefit patients by demonstrating a decrease in death and hospitalizations due to cardiovascular causes.

In the case of transcatheter revascularization, evidence from controlled clinical studies is low in heart failure; however, data derived from real-life studies are clear and allow these procedures to be considered as a useful therapeutic option for invasive management of coronary artery disease.[4,163]

From this positioning ***it is suggested that myocardial revascularization through the interventional or surgical procedures should be considered within a multidisciplinary medical team (Heart Team)*** in patients with ischemic HF in whom these procedures are considered to be suitable for angina relief or to decrease outcomes such as death and cardiovascular-cause hospitalizations. Therefore, whenever possible, these patients should be treated in centres with experience, and human and technological resources in terms of myocardial revascularization procedures.

It should be noted that coronary anatomy alone should not be the main criterion for the decision of such procedures. Therefore, it is advisable to make an assessment of the myocardial viability prior to invasive management decision through methods such as stress echocardiography, cardiac magnetic resonance imaging, nuclear medicine through the use of single photon emission computed tomography (SPECT), and in cases where positron emission tomography is feasible through the use of 18F-fluorodeoxyglucose (18-FDG-PET).[163]

2. MitraClip

Secondary mitral regurgitation is a condition that aggravates the prognosis of heart failure with reduced ejection fraction patients. Remodeling with the loss of ventricular geometry and dilation of the mitral ring are common in cases of HF-rEF transiting from moderate to advanced disease. As supported in this document, the detection and study of mitral regurgitation is important in the evaluation of patients with HF-rEF.

The use of devices for transcatheter repair of mitral regurgitation such as MitraClip has shown in studies such as COAPT[165] and MITRA-FR[166] its potential to decrease the degree

of mitral regurgitation and improve patient symptomatology. However, their use should not yet be considered as a standard management and indications should follow the same line of the selection criteria of the original studies, fundamentally discarding those patients with organic mitral valvulopathy or those who have a very limited life expectancy.

This positioning ***recommends that patients with HF-rEF who are considered potential candidates for MitraClip implantation be evaluated in specialized centers and that the final decision should be taken in consensus of a heart team*** in order to maximize the potential benefits of this procedure. At no time should the procedure be performed without a thorough prior evaluation involving noninvasive cardiovascular imaging studies (including 3D echocardiogram) and prior invasive hemodynamic study.

Similarly, ***the growth and expansion of centers specializing in high-specialized invasive procedures such as the MitraClip must be advocated***.

3. TAVI (transcatheter aortic valve implantation)

Heart valve diseases are one of the leading causes of heart failure. Aortic stenosis in the presence of heart failure is a condition that is commonly seen today.

One of the main challenges is presented by patients with left ventricular dysfunction and «low flow and low gradient» aortic stenosis; i.e. those with an aortic valve area < 1 cm^2, LVEF < 40%, and an aortic transvalvular gradient of < 40 mmHg. In these cases, there is a lack of definition about medical action with information from rest echocardiographic studies. For this reason, ***the use of stress echocardiogram with pharmacological stimulation protocol with dobutamine at low doses is suggested to define whether aortic stenosis is moderate or severe and to evaluate the contractile reserve.***[167]

In Heart Failure patients in whom severe aortic stenosis is concluded, in which medical treatment offers no or limited benefit and are not candidates for aortic valve replacement surgery, the implantation of a transcatheter aortic prosthesis (TAVI) is an option to consider.

The decision of a TAVI in the context of HF should be supported by an in-depth study of the aortic and coronary valve anatomy as well as the vascular accesses and clinical, hemodynamic, renal, haematological and frailty conditions of each of the candidates. In addition, in patients with HF-rEF, the risk of complications is comparatively greater than in those with HF-pEF and HF-mrEF[167] ***so the indication of a TAVI should always be made in the context of a joint decision by a heart team*** and the procedure should be performed by specific trained staff and in hospitals that have sufficient human and technological resources.

4. Mechanical circulatory assistance. This topic will be covered in the chapters of acute and advanced heart failure

IV. ACUTE HEART FAILURE

Acute heart failure (AHF) includes a series of clinical syndromes characterized by symptoms and signs of severe heart failure that occur in the form of pulmonary or systemic congestion with or without low cardiac output and are the product of hemodynamic overload or acute heart damage. It is a serious life-threatening condition for patients so it requires immediate diagnosis and early treatment. The purpose of this consensus is not to make an extensive review of the AHF, but to highlight the most outstanding aspects to improve its timely diagnosis and treatment.

From a clinical point of view, AHF may express as congestive symptoms at pulmonary and/or peripheral level as well as tissue hypoperfusion data denoting acute decrease in effective cardiac output. Pivotal data include the progression of the degree of dyspnoea to advanced functional classes, hydrosaline retention with the presence of lung crepitus and peripheral edema, and arterial hypotension, sensory alterations, decreased uresis, and diaphoresis can be found among other low cardiac output data in advanced cases.[168,169]

AHF can be classified from different perspectives, but for practical purposes two large groups of patients may be considered: Those without prior heart disease and who

Table 14: Acute Heart Failure common causes.

De novo acute HF	Chronic decompensated HF
• Acute ischemia • Hypertensive uncontrol (acute flash pulmonary edema) • Inflammation/infection (myocarditis, myopericarditis, endocarditis) • Toxic (drugs, toxic substances) • Acute valve dysfunction (endocarditis, acute ischemia) • Mechanical (septal rupture, acute mitral regurgitation, thoracic trauma, aortic pathology) • Arrhythmias (tachy or bradyarrhythmias) • Takotsubo syndrome • Acute cerebrovascular events • Acute renal failure • Thrombosis	• Transgression (farmacologic or alimentary) • Disease progression • Arrhythmias (tachy or bradyarrhythmias) • Infections • Acute ischemia • Uncontrolled hypertension hipertensivo • Drugs • Acute renal failure

HF = Heart Failure.

develop heart failure for the first time *(de Novo Acute Heart Failure)* and those who suffer a decompensation of their chronic HF *(Decompensated Chronic Heart Failure)*. The causes of de Novo AHF as well as chronic HF decompensation are summarized in *(Table 14)*. Among them acute ischemia and chronic treatment transgressions stand out for their high frequency. ***It is essential to have structured protocols for the immediate management of acute coronary syndromes, as well as patients and family members empowerment to ensure treatment adherence of chronic HF patients***.

Diagnosis of AHF should be expeditious, as early treatment and prognosis of patients depend heavily on this.

AHF diagnosis requires information derived from clinical, electrocardiographic, cardiovascular imaging and biochemical marker data. *Table 15* summarizes basic elements to be examined for the diagnosis of acute heart failure. It is important to note that ***a single data in isolation does not confirm or exclude the diagnosis of acute heart failure.*** It is therefore paramount to integrate a diagnosis through careful and rapid analysis of clinical and paraclinical data. This requires training and experience particularly in emergency services,[170] so from this positioning ***it is proposed to improve education to health personnel responsible for emergency services in order to have necessary professional skills for the AHF timely diagnosis.*** Also, ***any emergency service must have the basic elements for acute heart failure diagnosis***, among them, electrocardiography at rest, chest radiographic studies, and biochemical markers (natriopeptides, troponins), and ideally access to echocardiography and pulmonary ultrasound. Once the diagnosis is integrated it is necessary to implement the specific therapeutic measures in the shortest possible time. Currently parameters such as endovenous door-diuretic time for the management of patients with congestive AHF are indicators of quality, because it has been shown that dilation in diagnosis and treatment is directly proportional to the development of complications and adverse outcomes in AHF patients.[170]

AHF management should focus as much as possible on dealing with the direct cause of decompensation; for example, in the case of ST-elevation acute myocardial infarction, the best strategy will be the immediate implementation of myocardial reperfusion protocols in order to reduce the extent of damage and heart failure severity; in case of tachyarrhythmias, management will be aimed on controlling heart rate, in hypertensive crises with development of extreme diastolic dysfunction and pulmonary edema, treatment will be the rapid blood pressure control, in cases of severe pulmonary thromboembolism management will be thrombolysis and anticoagulation. However, despite these measures, there are conditions in which either the specific cause is not identified or despite being treated patients persist with acute ventricular dysfunction data. For this reason, the current Clinical Practice Guidelines propose a syndromic approach based on knowledge of patient's clinical-hemodynamic profile.[4] Thus, 4 profiles have been recognized according to two specific criteria:

1. Presence or absence of pulmonary or systemic congestion.
2. Presence or absence of tissue hypoperfusion (low cardiac output).

Figure 24 summarizes the four profiles according to the heart failure clinical-hemodynamic characterization.

Most common profile is *«warm and wet»* patients which refers to those with the presence of pulmonary and/or systemic congestion without low output data.[171,172] Examples include patients with chronic heart failure decompensated by dietary transgressions or drug treatment. In these cases, management will be aimed at defining whether the predominance of the affectation is cardiac or vascular; thus, in the first scenario the fundamental management will be the use of diuretics, while the latter (e.g. Hypertensive emergency with acute pulmonary edema), then initial treatment should consider the use of endovenous vasodilators. On the other hand, if the profile is of *«cold and wet»* patients, i.e. those with congestion and hypoperfusion, the initial therapeutic orientation should include the use of inotropics, in cases of severe hypotension endovenous vasopressors may be used, and in cases refractory to pharmacological management, mechanical circulatory assistance offers an alternative, especially with the development of technologies such as ECMO (extracorporeal membrane oxygenation).[4,173] *Figure 25* summarizes the comprehensive approach to Acute Heart Failure *and Table 16* doses of diuretic and vasoactive agents for pharmacological management.

While it is true that AHF treatment is useful for improving patient acute engagement, its impact on medium- and long-term prognosis is now good or even null. In recent decades numerous controlled clinical trials have been conducted trying to demonstrate that management with vasodilators (nesiritide[174]), inodilator (levosimendan[175,176]), cardioprotective (serelaxine[177]) or with other effects (tolvaptan,[178] rolofiline[179]) could have a beneficial impact on patients' survival in

Table 15: Basic elements to be assessed for acute heart failure diagnosis and stratification.

Test				
Clinical	Electrocardiography	Chest x-ray	Ultrasound	Biochemical markers
• Dyspnea • Lung congestion • Tachypnea • Abnormal ventilatory mechanics • Jugular plethora • Peripheral oedema • Changes in blood pressure • Neurological status alterations • Abnormal temperature (fever, hypothermia) • Pallor • Diaphoresis • Pulse characteristics • Cyanosis	• Acute ST segment changes • QRS width • Voltage drop • Brady or tachyarrhythmias • AV conduction disturbances	• Cardiomegaly • Pulmonary congestion (Kerley lines A and B) • Pleural effusion • Mediastinal widening	Echocardiogram • Impaired mobility/ torsion • Structural alterations (valve dysfunction, vegetations, free wall rupture, septal rupture) • Intracardiac Thrombi • Hemodynamic estimations • Study of great vessels • Pulmonary ultrasound • Pulmonary congestion	• Natriuretic peptides • Troponins • Glycemia • Serum creatinine • Ureic nitrogen • Arterial gasometry • Liver function tests

AV = atrioventricular.

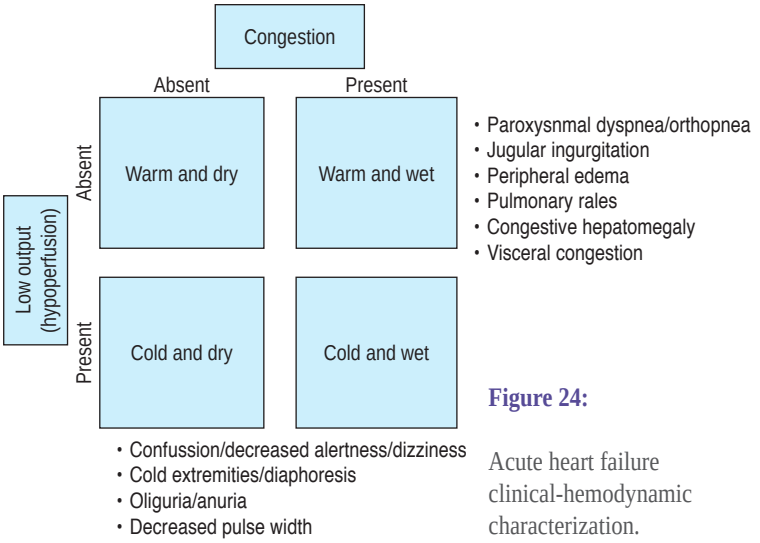


Figure 24:

Acute heart failure clinical-hemodynamic characterization.

medium and long term. So far all these trials have failed to demonstrate this effect. On the other hand, the use of conventional inotropics such as dobutamine or milrinone has proved controversial and its effects in the medium and long term are arguable. Therefore, the contemporary approach for the management of acute heart failure requires an understanding of two fundamental concepts: a) Vulnerable phase, and b) disease-modifying treatment.

1. **Heart Failure vulnerable phase.**[180] It refers to the period of time ranging from the acute stage of the disease and up to 3-6 months of hospital discharge. It has been recognized as the period with the highest risk of relapse and mortality, according to the natural history of the disease. On the other hand, it is also considered as the time when therapeutic measures may be implemented to improve the clinical course in the medium and long term. Therefore, ***the vulnerable phase in heart failure represents the best opportunity window for optimizing long-term HF treatment.*** *Figure 26* outlines the natural history of Heart Failure throughout the vulnerable period.
2. **Disease-modifying treatment.** These are all therapeutic measures that are implemented with the purpose of prolonging quality life of heart failure patients. Regarding medicines, sacubitrile/valsartan, ACE inhibitors, beta blockers, angiotensin receptor blockers, mineralocorticoid antagonists, ivabradine and more recently SGLT2i are included in this area. For devices, cardiac resynchronization therapy, implantable automatic defibrillators, and mechanical circulatory assistance as target therapy are measures that may improve clinical course of HF and its prognosis. Non-pharmacological measures are also vital for improving the quality of life and functional capacity of patients with HF. Therefore, ***it is essential that every HF patient during the vulnerable phase initiates or optimizes the disease-modifying treatment.*** To do this, it is necessary to implement safety mechanisms such as the use of checklists for the pre-discharge period of hospitalized patients and to ensure that no patient lacks the basic medication for the HF chronic phase.[181] In addition, patients who are dicharged from hospital after an episode of AHF should have a follow-up scheme to allow the early titration of disease-modifying drug doses as well as the early definition of candidates for an implantable device. To achieve this goal is desirable, whenever possible, that patients are admitted to structured programs for the management of heart failure or to have care protocols that function as a way of clinical action to guide have protocols of care that function as a way of clinical action to guide a timely integration of a comprehensive treatment capable of favorably modifying disease course if there is no heart failure clinic available. *Figure 27* summarizes proposal management for vulnerable disease phase. In conclusion, it can be said that the ***treatment of chronic heart failure is the best treatment of acute heart failure.***

V. ADVANCED HEART FAILURE

Advanced Heart Failure refers to patients with clinically significant circulatory involvement and persistence of symptoms that severely limit daily life (NYHA FC III-IV) despite optimized medical treatment (OMT).[182]

Patients with advanced HF are estimated to comprise between 1 and 10% of all Heart Failure patients and prevalence is increased

with a higher number of HF patients, treatment improvements, and increased survival.[182] Patients with advanced or OMT refractory HF have high morbidity, and cardiac transplantation (CT) is the only treatment option that reaches an improvement, but can only be applied to a small number of patients; for this reason, mechanical circulatory support has become one of the best alternatives for patients with advanced HF.[182]

Due to its severity and high mortality, the treatment of advanced or terminal heart failure (HF) should be provided **only** by Cardiologists and/or Cardiovascular Surgeons **specialized** in HF and Cardiac Transplantation in Cardiology Centers for the care of this pathology in the country.

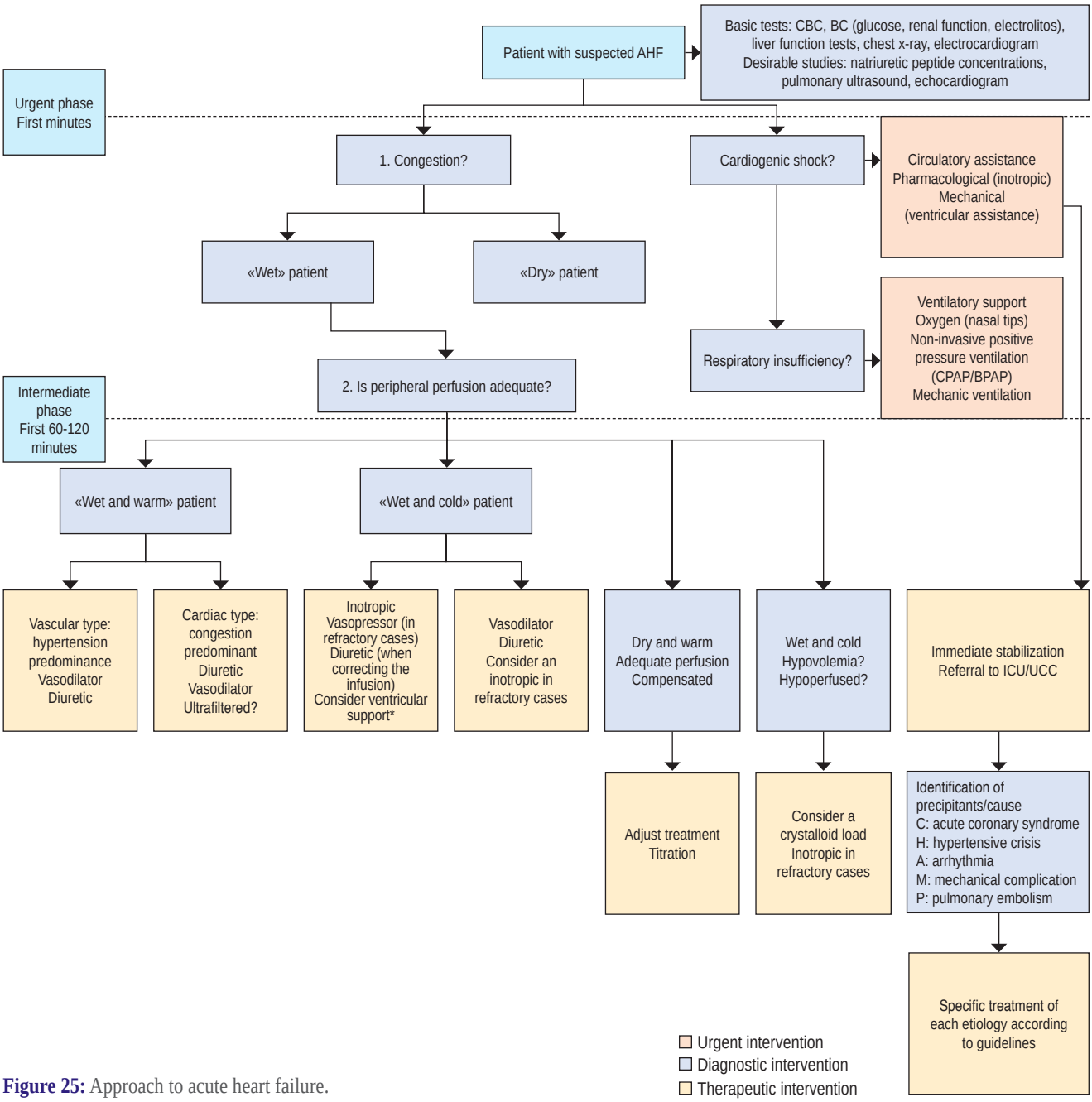


Figure 25: Approach to acute heart failure.

Tabla 16: Diuretic agents, vasodialators, inotropics and vasopressors for the management of acute heart failure.

Drug	Bolus	Dose adjustments
Furosemide	20-40 mg IV	400-600 mg/day
Nitroglycerine	No	Initial dose10-20 µg/min (initiate) Maximum dose 200 µg/min
Nitroprusside	No	Initial dose 0.3 µg/kg/min Maximum dose 5 µg/kg/min
Dopamin	No	3-5 µg/kg/min (inotropic dose)
Dobutamin	No	2-20 µg/kg/min
Milrinone	25-75 µg/kg en 10-20 min	0.375-0.75 µg/kg/min
Levosimendan	12 µg/kg/min en 10 min (optional)	0.1 µg/kg/min (0.5 µg/kg/min - 0.2 µg/kg/min
Norepinephrine	No	0.2 - 1.0 µg/kg/min

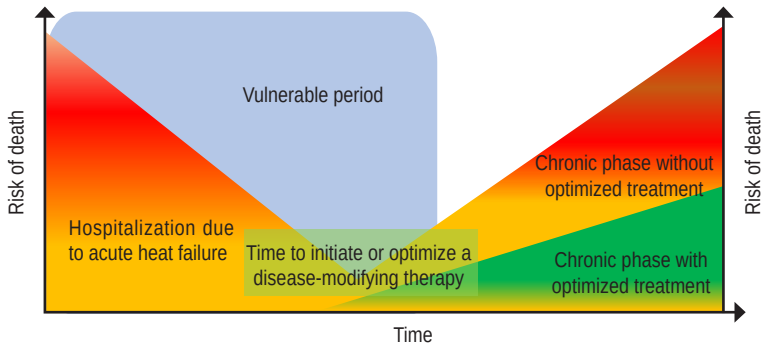


Figure 26: Vulnerable phase in heart failure and time for initiation or optimization of disease-modifying therapy.

It is important that physicians can identify patients with advanced HF early to adjust treatment or, where appropriate, refer them to centers that can provide high specialty therapeutic alternatives. To this end, operational definitions have been created wich through specific criteria allow us to identify these patients.[182] *Table 17* summarizes the elements to diagnose advanced HF.

Once the diagnosis is made, there are several therapeutic alternatives according to each patient profile. These include: a) Programmed decongestant therapy, b) Intermittent inotropic therapy, c) Mechanical circulatory assistance devices, d) Cardiac transplantation, and e) End-of-life care and thanatological intervention.

1. Programmed decongestant therapy

In advanced HF patients it is common for oral medications to decrease their efficacy, particularly in case of diuretics.[183] This is due to a decrease in intestinal absorption, and to splanchnic congestion. Additionally, pharmacokinetic parameters are altered if there is evidence of added hepatic or renal dysfunction. As a result, many patients present a worsening of congestive symptoms and require specialized interventions. The use of programmed endovenous diuretic therapy is an alternative for progressive or refractory congestion management. Since parenteral use of diuretics requires close monitoring of blood pressure, renal function and serum electrolytes, it is not advisable consider this kind of management in offices or facilities without guaranteeing patients safety. Thus, ***the creation of infusion centers or in-day hospitals are an option for the use of programmed endovenous diuretic therapy as a decongestion strategy in patients with advanced HF***. In case of resistance to diuretics, ultrafiltration should be considered as an alternative; although this procedure requires high specialty medical units to be implemented.

2. Scheduled inotropic therapy

The use of conventional inotropics (dobutamine, milrinone) in chronic management of heart

failure has not shown long-term benefit for patients. So their routinely use is not currently recommended.[4] However, inodilators such as levosimendan have demonstrated a potential for benefit in small randomized studies and meta-analyses.[184,185] Pharmacokinetic characteristics of this drug (long-lasting effect, lack of a weaning protocol) make it attractive for intermittent administration. In the LION-HEART[184] study, infusion of levosimendan at doses of 0.2 µg/kg/min for six hours every 2 weeks for 12 weeks in patients with advanced HF demonstrated a decrease in NT-proBNP levels as well as a favorable trend in decrease in hospitalizations for decompensated HF. ***In patients with advanced HF it is reasonable to consider intermittent administration of inodilators as an alternative to improve quality of life.*** As with intermittent use of IV diuretics, inodilators administration should be contemplate in infusion centres or ambulatory hospital programmes in order consider close monitoring and to increase patient safety.

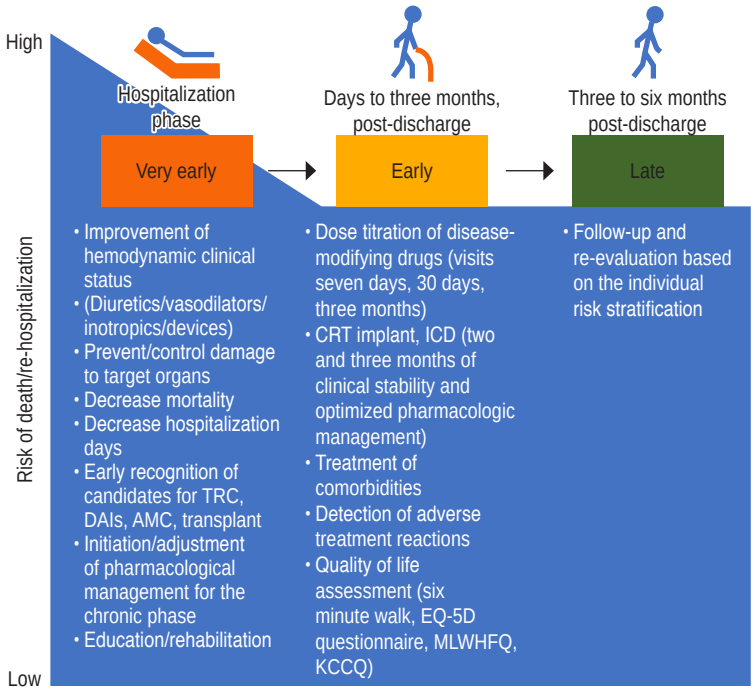


Figure 27: Acute heart failure vulnerable period management from hospital to home. CRT = cardiac resynchronization therapy, ICD = implantable cardiac defibrillators.

3. Mechanical circulatory assist devices

In patients with advanced HF where drug treatment is insufficient to achieve clinical stability or impact on prognosis, mechanical circulatory assist (MCA) can be considered as a high specialty alternative for patient management.

In order to do this, it is essential to adequately identify candidates for such therapy. ***Classification of the Inter-Agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a useful tool for defining those patients who will benefit from MCA***

Table 17: Advanced heart failure diagnosis elements.

- Persistent NYHA functional class III-IV despite optimized maximum treatment
- Distance covered in a six min walk < 300 m
- LVEF < 30% or isolated right ventricular failure (VD)
- Severe congenital or valve abnormalities not suitable for surgical correction
- Elevated ventricular filling pressures (cardiac catheterization)
- Persistently elevated BNP or NT-pro BNP
- Severe structural alteration of LV or RV
- Recurrent hospitalizations due to chronic heart failure decompensation episodes that required IV diuretics or inotropics or severe arrhythmias that condition one or more hospitalizations in the last 12 months
- VO_2 < 12 or 14 mL/kg/min
- Significant multi-organ damage as a consequence of chronic heart failure

NYHA = New York Heart Association, LVEF = left ventricular ejection fraction, BNP = B type Natriuretic Peptide, NT-proBNP = amino terminal pro B natriuretic peptide, LV = left ventricle, RV = right ventricle, IV = intravenous, VO_2 = oxygen consumption.

Table 18: INTERMACS classification for advanced heart failure.

	Profile	Characteristics	Time for intervention
1	Critical cardiogenic shock	Severe, life-threatening hypotension unresponsive to escalating doses of inotropics or vasopressors, critical tissue hypoperfusion, progressive acidosis	The definitive intervention must be installed in hours
2	Progressive deterioration	Progressive deterioration of cardiac function despite inotropic treatment (dependence on inotropics) there may be multi-organ involvement, renal failure, cachexia)	The definitive intervention should be implemented within a few days after scenario 2 is declared
3	Stable patients but inotrope-dependent patients	Stable BP, multiorganic stability but inotropics dependent or with temporary circulatory support or both	Definitive intervention to be implemented in weeks
4	Symptoms at rest	Patients with significant limitation of their functional capacity but close to euvolemia. Dependent on high doses of diuretics	Definitive intervention to be implemented in weeks or months
5	Exercise intolerant	Comfortable at rest but with poor or no tolerance for physical activity. It is advisable to measure VO_2 to make physical limitation objective	Variable, dependent on nutritional status, multi-organ involvement and degree of physical activity required
6	Limited physical activity	Comfortable at rest but with significant limitation to physical activity or exercise. It is convenient to measure VO_2 to make objective physical limitation	
7	Advanced NYHA class III	Stable, no multi-organ damage, no major changes in functional class but with significant physical limitation	No indication for heart transplantation or mechanical circulation assistance

NYHA = New York Heart Association.

devices. There is a clear benefit of circulatory support in patients with INTERMACS 1, 2, and 3 profiles, without being so clear for the other stages, so these patients should be carefully selected[186] *(Table 18)*.

By support time, ventricular assist devices (VADs) are classified as short- (days to weeks) or long-lasting (months to years). There are four MCA indications, depending on those, the device will be chosen based on its duration and support features.

Indications for mechanical circulatory assistance: bridge to recovery, bridge to cardiac transplantation, bridge to decision, and finally as destination therapy. In first two indications, the patient is a potential candidate for cardiac transplantation (CT); destination therapy (DT) is reserved for patients who are not CT candidates, so that patient will be subjected to a long-lasting device as the patient will live while receiving assistance of a VAD.[187,188] The following are the current indications for MCA:

a. **Bridge to recovery.** It is an indication for acute and severe heart conditions (post-infarction or post-cardiotomy cardiogenic shock, acute myocarditis, acute post CT graft dysfunction, etc.) where the VAD is placed in order to make the assisted ventricle rest trying to regain its functionality to the extent that it allows the device to be withdrawn. Ventricular assistance as a bridge to recovery includes short-term devices such as Centrimag, extracorporeal life support

(ECLS) in non-hypoxemic patients (mostly), Extracorporeal membrane oxygenation (ECMO) for patients with concomitant severe oxygen disorder (infrequent in HF). If such recovery is not achieved, the VAD will switch to bridge-to-CT indication or will be migrated to a longer-term VAD to establish the DT indication.

b. **Bridge to heart transplant.** THE VAD is placed to assist patient's heart and take him/her to a cardiac transplantation waiting list. For this purpose, it is necessary to consider the waiting time to get the heart for the transplant in each region or country. In Mexico, for example, a **zero priority** patient can be transplanted in a period even shorter than 15 days. Therefore, in this specific circumstance it is preferred to use a short-duration and therefore lower-cost device which is very appropriate for the economic reality of the country. In Mexico, Centrimag, ECLS or ECMO may be selected first instance; for cases where the waiting time will be prolonged, a long-lasting VAD such as Heart Mate 3 or HeartWare will be considered.
c. **Bridge for decision**. Indication reserved for patients in critical condition, with severe organic damage or with uncertain neurological status where the adequacy for a CT is not clear (severe HF with severe renal or liver damage, post-cardiopulmonary resuscitation status, etc.). A short-term (and lower cost) VAD is chosen to provide circulatory support potentially capable of improving clinical and organic conditions that clarify patient's candidacy for CT such as Centrimag, ECLS or ECMO (if this is achieved, change the indication for bridge to CT), if the organ is not available, migrate it to a chronic VAD (Heart Mate II, Heart Mate 3, or Heart Ware) as a bridge to CT or DT.
d. **Destination therapy.** This indication applies to patients with terminal HF who are not initially candidates for CT, so they require a long-lasting VAD. Currently only 3 VADs are authorized by the Food and Drug Administration (FDA) to be used as Destination Therapy: Heart Mate II, HeartWare, and Heart Mate 3. All provide chronic assistance (even for years), Heart Mate II and HeartWare provide continuous flow while Heart Mate 3 provides a continuous pulsatile flow. Heart Mate 3 and HeartWare are placed intrapericardially allowing placement surgery to be less invasive. These three devices are very expensive; however, there is national experience, although limited but successful, in some centers in both public and private health sectors with Heart Mate II and Heart Mate 3 as destination therapy.

Whatever indication may be, MCA should be instituted immediately after clarifying its need, since less severe patient condition is when placing the VAD, a better result is expected after care period.

4. Heart transplant

Human cardiac transplantation is a major surgical procedure that came true 50 years ago with the first successful transplant in South Africa by Dr. Christiaan Barnard. In Mexico, first heart transplant was performed in 1988 at the «La Raza» Medical Center of Instituto Mexicano del Seguro Social by Dr. Rubén Argüero Sánchez. After five decades of development and innovation in surgical techniques, perioperative management, immunosuppressive schemes and management of acute and chronic complications, cardiac transplantation has established itself as the preferred option for patients with terminal heart failure in whom the therapeutic options described so far are insufficient to modify the clinical course of the disease, and to improve short-term life prognosis.

One of the main challenges in Heart Transplantation is the appropriate selection of patients. The question is therefore relevant:

When should a patient be considered a cardiac transplant candidate?

The presence of severe myocardial damage (LVEF < 30%) alone does not justify the indication of a cardiac transplantation. This is because there are proven therapeutic alternatives that can increase life expectancy with quality and should be consider in these patients before defining the indication of transplantation.

While there are multiple scenarios in which cardiac transplantation should be considered, in practice the following aspects must be consider:

1. **Refractory HF:** it must be confirmed that HF patient does not respond to treatment. The main points to consider are:

    a. Reversible or specific treatment-susceptible heart disease has been ruled out: myocarditis in resolution phase, ischemic heart disease, valvulopathies, tachycardiomyopathies, etcetera.
    b. Patient must have received optimal drug treatment for a reasonable time at maximum tolerated doses.
    c. All options that may improve patient's functional class have been exhausted: treatment of iron deficiency, cardiac resynchronizer, cardiac rehabilitation, second-line medications, etcetera.

2. **Prognosis estimation:** patients with good prognosis (e.g. in functional class I and II) are not considered for cardiac transplantation. In contrast, patients in functional class IV, or functional class III with high-risk data, are patients to be evaluated for transplantation. Risk scales such as the Heart Failure Survival Score or the Seattle Heart Failure Score[189] are useful for guidance regarding one-year mortality risk. An estimated survival of less than 80% at one year should be a strong indicator of transplantation need; however, these scales are merely indicative and cannot be considered an absolute criteria for defining a transplant indication. In general, patients who meet the definition of advanced heart failure should be evaluated for cardiac transplantation. Other points that may indicate a transplant include:[4,190]

    a. Repeated hospitalization due to symptom progression in recent months.
    b. Progressive cardiac cachexia.
    c. Initial impairment of kidney or liver function.
    d. Heart rate < 2.2 L/min/m^2BS, malignant ventricular arrhythmias, oxygen consumption of less than 14 mL/kg/min, or a distance walk on the 6-minute walk test < 300 meters.

3. **Comorbidities:** the presence of comorbidities may affect post-transplant results. Each centre should define its own criteria about what comorbidities may be considered as absolute or relative contraindications, but the assessment should include age (fragility rates), obesity, diabetes mellitus, renal function, cancer, pulmonary hypertension, brain or peripheral vascular disease, toxic substances abuse, HIV infection, hepatitis.

4. **Psychosocial evaluation:** this aspect is as important as the previous three, since in many ways it defines the possibility that a patient can be psychologically prepared to receive the graft from the cadaveric donor and comply with the post-transplant therapeutic attachment. Aspects to be considered in a psychosocial evaluation pre-transplantation are:

    a. Patient has social support before, during and after the transplant. Usually social team work takes care of this point.
    b. There is no history of addictive substance abuse (alcohol, tobacco, drugs, etc.), or there is evidence that patients have been free of addictions for one year (each center defines its own criteria), and a psychological/psychiatric evaluation excludes high risk of addiction recurrence.
    c. The patient adheres to treatment and meets follow-up visits: as previous point, psychological/psychiatric evaluation is of high importance in identifying patients at high risk of treatment cessation or follow-up.

Absolute contraindications for cardiac transplantation include:

1. Systemic diseases with life expectancy under one year regardless of heart failure.
2. Malignancies with high chance of recurrence.
3. Diabetes mellitus with development of advanced non-recoverable target organ damage.

4. Irreversible severe pulmonary hypertension.
5. Severe chronic obstructive pneumopathy (forced vital capacity < 50%).
6. Uncontrolled septic status.
7. Severe non-recoverable neurological disease (Alzheimer's, severe sequelae of previous brain vascular events).
8. Advanced biological age with life expectancy under three years.

Relatively, cardiac transplantation is discouraged in cases of:

1. Obesity, BMI > 35 kg/m^{2}SC.
2. HIV infection.
3. Light or moderate cerebral atherosclerosis without severe physical limitation.
4. Renal failure under replacement therapy (the possibility of cardiac and renal transplantation should be considered).
5. Liver cirrhosis (heart and liver transplantation may be considered).
6. Chronological age > 65 years (each centre shall establish this criteria and in conjunction with the multidisciplinary evaluation define if transplantation in older patients is indicated).

Once all clinical, paraclinical, cardiological and multidisciplinary evaluations information is gathered, patients with advanced heart failure who are considered as ***cardiac transplant candidates should be presented to a transplant committee*** in order to evaluate each particular case from a multidisciplinary point of view and decide whether or not to include the patient in a waiting list and assign as priority for transplant. From a legal point of view, cardiac transplantation decision may never be based on a one-person criteria or defined in partial assessments.

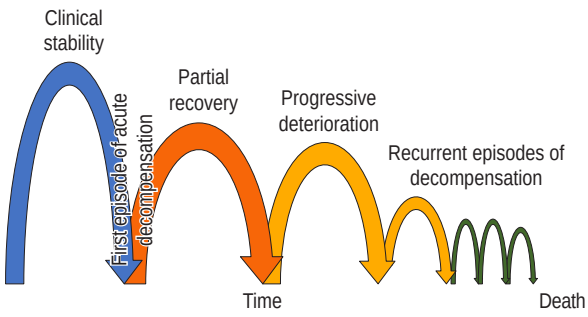


Figure 28:

Heart failure natural history.

The decision of surgical technique and immunosuppression schemes shall be defined by each transplant programme and in accordance with national and international transplant recommendations.[4,191]

Currently, records from the International Heart and Lung Transplant Society state that the average survival after a heart transplant is around 11 years.[192] For this reason, structured programmes are needed to ensure patient safety and overall procedure results.

Since cardiac transplantation is a highly complex procedure, and patients require specialized perioperative and long-term care***, it is imperative that units performing heart transplantation have the hospital infrastructure, trained and experienced health personnel, as well as a structured HF program for patient monitoring throughout their evolution***. Similarly, all requirements established in the legal and regulatory framework for the conduct of organ and tissue transplants (health licenses, health personnel competency registers, structured care protocols, formation of transplant committees, incorporation of transplant programs into institutional, national and regulatory bodies) should be available.

5. Palliative care in advanced heart failure

Heart failure is a progressive disease. Natural history of the disease exhibits a downward curve that begins with the first episodes of decompensation and is followed by multiple events of sharpening, deterioration and progression of myocardial and multiorgan damage that lead to a fatal outcome in the end *(Figure 28)*.

Comprehensive heart failure treatment has been able to extend quality life expectancy in many heart failure patients; however, in a significant number of cases the disease will progress to terminal stages.

In patients with advanced heart failure who are not candidates for cardiac transplantation or circulatory assist devices as destination therapy and those with short term life expectancy, it is necessary to implement measures to improve quality of life in latter life phase.

For this reason, ***it is essential to identify patients with end-stage HF.*** *Table 19*

Table 19: End-stage heart failure characteristics.*

Clinical characteristics	Paraclinical	Functional testing
• Advanced age (> 70 years) • Persistent NYHA functional class IV • Poor tolerance to oral medication requiring its suspension • Persistent congestion despite use of diuretics • Electrical instability (recurrent arrhythmias) • Frequent ICD downloads • Severe or symptomatic hypotension • Ischemic etiology not susceptible to revascularization or incomplete or non-functional revascularization • Cardiac cachexia • Advanced renal failure • Depression/dysthymia/anxiety • Recurrent hospitalizations in which each one is longer and the decompensation-free period is shorter • Patient not a candidate for heart transplantation or mechanical circulatory assist	• LVEF < 30% • Resting tachycardia • Increased QRS widening • Hyponatremia • Decreased eGFR < 30 mL/min/1.73 m^2SC • Persistent elevation of natriuretic peptides • Severe mitral regurgitation not suitable for repair • Non-reversible increase in pulmonary vascular resistance (Wood units > 5)	• VO_2 < 12 mL/kg/min • Distance covered in 6 min walk test < 200 m

LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, QRS, ICD = implantable cardioverter defibrillators, VO_2= oxygen consumption.

summarizes patient with advanced end-stage HF characteristics.

In oncology, palliative care and thanatological support have well managed suffering reduction of patients in terminal disease stages; however, in Cardiology, palliative care programs are scarce, so the creation of palliative care programs for patients with advanced HF who ***are not susceptible for disease-modifying treatments should be encouraged.***

Studies such as PAL-HF[193] *(Palliative Care in Heart Failure) or* SWAP-HF[194] (Social*Worker-Aided Palliative Care in High-risk Patients with Heart Failure)* showed that a multidisplinary intervention is able to improve quality of life in patients with advanced HF; in the same way, a decrease has been shown in states of anxiety and depression which frequently accompany patients at this disease stage.

Interventions in a structured palliative care program in Heart Failure should consider:[4,193]

a. **Maintenance, optimization or suspension of pharmacological management.** A common feature in end-stage heart failure is a lack treatment tolerance. Particularly due to hypotension or paradoxically by symptoms worsening. Therefore, it is needed to rethink the usefulness of medications and to adjust combinations, doses and, in cases where it is concluded that, after a formal evaluation, patients are effectively in their disease end stage and their life expectancy is very short (days-weeks), the suspension of disease-modifying therapy may be considered.
b. **Relief of dyspnoea and pain.** In cases where dyspnoea and pain superlatively affect the quality of life of patients with terminal heart failure. The use of oxygen therapy must be evaluated. Opioid use may also be an accessible option. In cases where life expectancy is very short palliative sedation may be considered. These decisions should be made in

conjunction with multidisciplinary groups as well as in concert with the patient's family members. Similarly, it is relevant, whenever feasible, to discuss end-of-life management decisions within bioethics committees and get their endorsement. It is desirable that, if the use of controlled medications is decided, they should be prescribed and monitored by health personnel with professional competences and experience in the use of these resources (algologists, anesthesiologists, geriatricians, thanatologists).

c. **Psychological and spiritual support.** Patients with terminal HF who maintain a state of consciousness usually present depression and anxiety. Therefore, psychological and psychiatric support may help to reduce the decline of these aspects in patient quality of life. Also, while religion can occupy an important place within the culture and vision of patients and their families, spiritual support is important to be considered.

d. **Nutrition.** Cardiac cachexia is a very common fact in patients with severe advanced HF and in those who are terminally ill. Nutritional assessment and food support are essential in a palliative care program. Also, the use of medication such as olanzapine or steroids can be considered as an adjuvant therapeutic measure.

e. **Decision making in patients with implantable defibrillators.** In end-stage patients, the usefulness of implantable defibrillators is limited or null. Therefore, in those patients whose life expectancy is very short (days-weeks), the withdrawal or inactivation of these devices may be assessed. As with other difficult-to-decide interventions, this measure must have patient´s, his family, and as far as possible, the consensus of bioethics committees approval.

f. **Thanatological support.** Thanatological measures implemented by professionals have proven to be useful not only for patients, but for their family environment. An expert evaluation is appropriate because it helps identify if the diagnosis of terminal disease is appropriate. In addition, the multidimensional approach to drug intervention is an invaluable aid to best face loss and duel, even in advanced way.

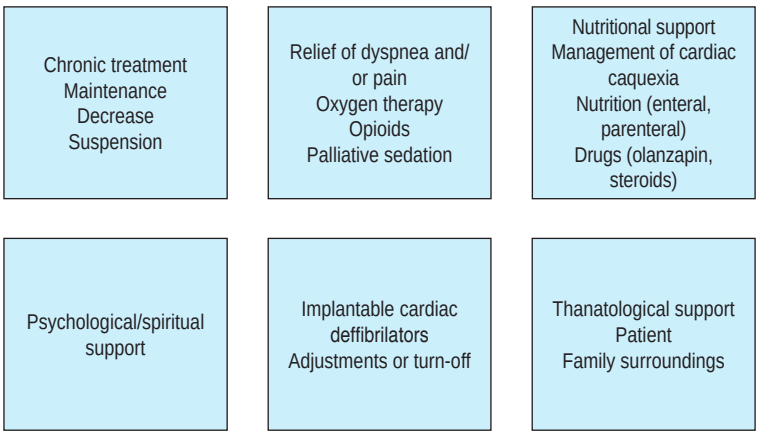


Figure 29: Comprehensive approach to end-stage heart failure patient.

Figure 29 summarizes interventions for palliative care in end-stage heart failure.

In conclusion, ***advanced heart failure is a challenge for doctors, patients, family members and health systems.*** Patients who meet advanced HF criteria need to be accurately identified in order to be early referred to specialized management facilities. Timely therapeutic interventions have shown improvement of disease course, and those end-stage patients who have achieved a reasonable quality of life improvement. Approach should always be within structured programs with a multidisciplinary methodology.

VI. HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart failure with preserved ejection fraction (HF-pEF) is a public health problem. Its frequency amounts to 50-60% of all patients with Heart Failure.[195] Even though the mortality of this condition is lightly lower than that observed in HF-rEF. HF-pEF causes a great limitation in the quality of life of those with it. Additionally, this problem is on the rise due to an increased life expectancy as well as an increased exposure time to entities such as diabetes, high blood pressure or obesity, that are an important source of HF-pEF.

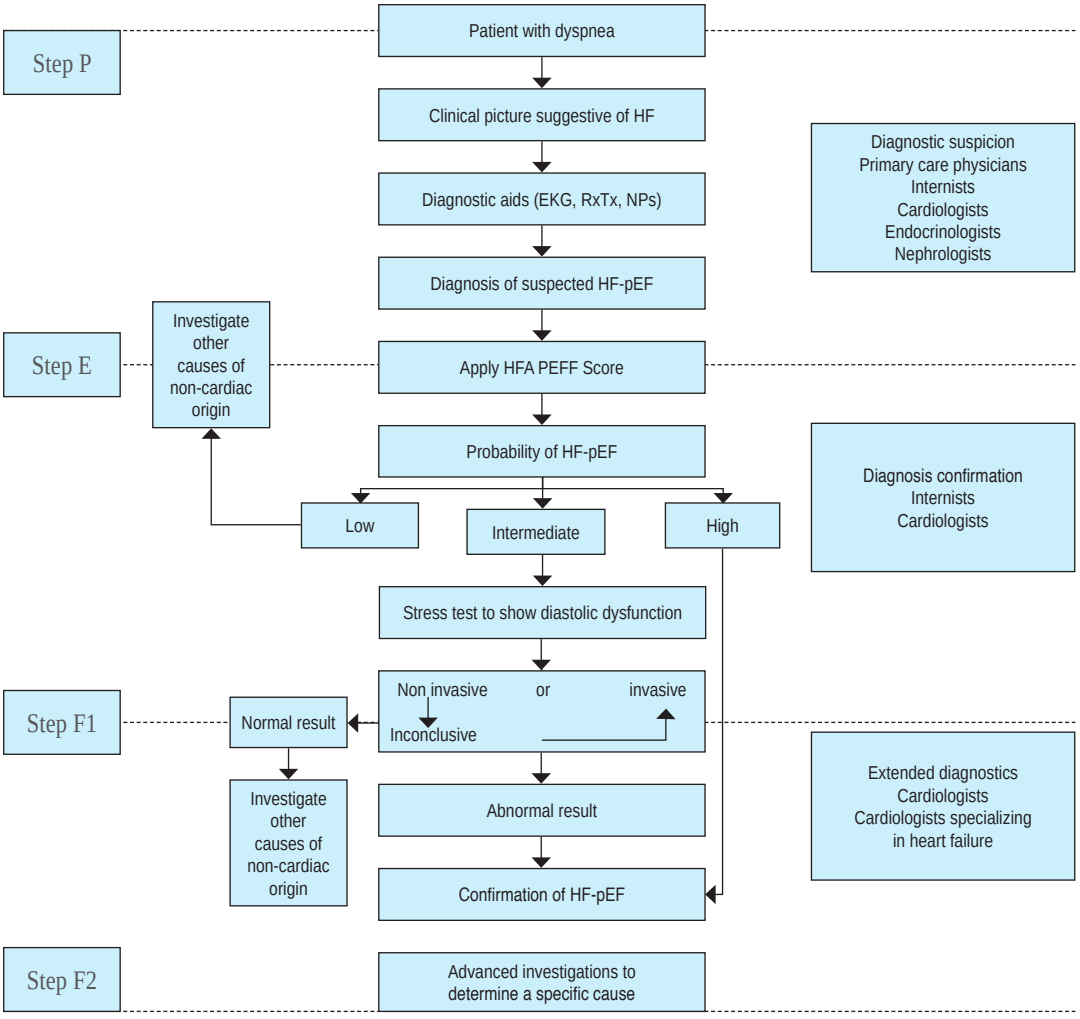


Figure 30:

Diagnostic algorithm for heart failure with preserved ejection fraction. EKG = Electrocardiogram, RxTx: Chest x Ray, NPs: Natriuretic peptides, HF-pEF = heart failure with preserved ejection fraction, HFA PEFF Score = Heart Failure Association HF-pEF diagnostic algorithm.

It is considered a different as well as a complementary condition of HF-rEF. Its physiopathology is complex and encompass functional and structural situations that go beyond diastolic dysfunction in isolation.[196]

For this reason, ***a clinical suspicion of the disease should be established at all medical care levels***, while special cases (e.g. Cardiac amyloidosis) must be referred to specialized centres.

Diagnosis of HFpEF constitutes a challenge for the clinician, and in order to increase precision and avoid overdiagnosing or underestimating cases of HFpEF, it is proposed that all patients with signs and symptoms suggestive of HF, and in complementary studies a LVEF ≥ 50% is calculated, the algorithm proposed by European HF Association should be used as an aid to increase the diagnostic precision of HF-pEF[197] *(Figure 30 and Table 20)*.

It is recommended to request clinical phenotype to every patient with a confirmed diagnosis in order to guide the treatment. The varieties to be considered are:[198]

1. «***Garden variety***» includes women, obesity, hypertension, diabetes and metabolic alterations where insulin resistance is a common factor.
2. HF-pEF of ischemic origin.
3. HF-pEF due to right ventricular failure and pulmonary hypertension.
4. HF-pEF with predominant atrial fibrillation.
5. High cardiac output HF-pEF.
6. HF-pEF due to cardiac valvular disease.

7. HF-pEF similar to hypertrophic cardiomyopathy.
8. Associated HF-pEF and renal disease.
9. Uncommon etiology HF-pEF (e.g. cardiac amyloidosis).

Once the phenotype is identified, it is suggested to consider the following general principles for the HF-pEF management:

1. Because no therapeutic option alone has been shown to be completely effective, treatment should be individualized according to the patient's clinical phenotype.
2. In cases with suspected restrictive or hypertrophic cardiomyopathy, complementary imaging studies (3D echocardiogram, cardiac magnetic resonance imaging, and genetic mapping) are necessary to clarify specific diagnosis and treatment.
3. It is important to maintain the euvolemic state and avoid the indiscriminate use of diuretics, particularly loop ones.
4. In every patient with HF-pEF it is essential to achieve an optimal treatment of morbid conditions (e.g. High blood pressure or Diabetes mellitus) as well as the etiology of the condition (myocardial ischemia, cardiac valvular disease).
5. Mineralocorticoid antagonists appear to be helpful in improving symptoms and clinical evolution of «*garden variety*» patients.[199,200]
6. Available evidence suggests that Sacubitril-Valsartan may be an option to improve the clinical course of women with HF-pEF, in patients with a LVEF of 57% or less and in those with concomitant use of mineralocorticoid antagonists.[201]
7. The use of Beta blockers or Ivabradine is not recommended as a general measure for HF-pEF treatment; however, in case of heart rate control need in these patients, it should be confirmed in advance that there is no chronotropic incompetence.[202]
8. Pulmonary vein ablation should be considered in cases of HF-pEF with uncontrolled atrial fibrillation with medications, whenever atrial fibrosis does not contraindicates the procedure.[203]
9. There is not sufficient clinical evidende for the use of SGLT2i and GLP1 analogues in non-diabetic patients with HF-pEF, so today their routine use is not recommended.

Table 20: HFA PEFF Score criteria for the diagnosis of heart failure with preserved ejection fraction.

	Variables			
Criteria	Functional	Morphologic	Biomarkers (sinus rythm)	Biomarkers (atrial fibrillation)
Major (2 points)	Septal e´ wave < 7 cm/s or lateral < 10 cm/s or E/e' ratio > 15 or IT speed > 2.8 m/s (PSAP > 35 mmHg)	Indexed left atrial volume (IAV) > 34 mL/m^{2}SC or Left ventricular mass index (LVMI) >149 g/m^{2}SC in men or 122 g/m^{2}SC in women	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	NTproBNP > 660 pg/mL or BNP > 240 pg/mL
Minor (1 point)	Ratio E/e' 9-14 or GLS < 16%	IAV 29-34 mL/m^{2}SC or LVMI > 115 g/m^{2}SC in men or > 95 g/m^{2}SC in women	NTproBNP 125-220 pg/mL or BNP 35-80 pg/mL	NTproBNP 365-660 pg/mL or BNP 105-240 pg/mL

Interpretation:
5 points or more: High risk = heart failure with preserved ejection fraction.
2-4 points: Intermediate risk: additional studies are suggested to demonstrate diastolic dysfunction on effort.
1 point or less: Low risk= Look for other causes of the clinical picture.
Pieske B et al.[197]

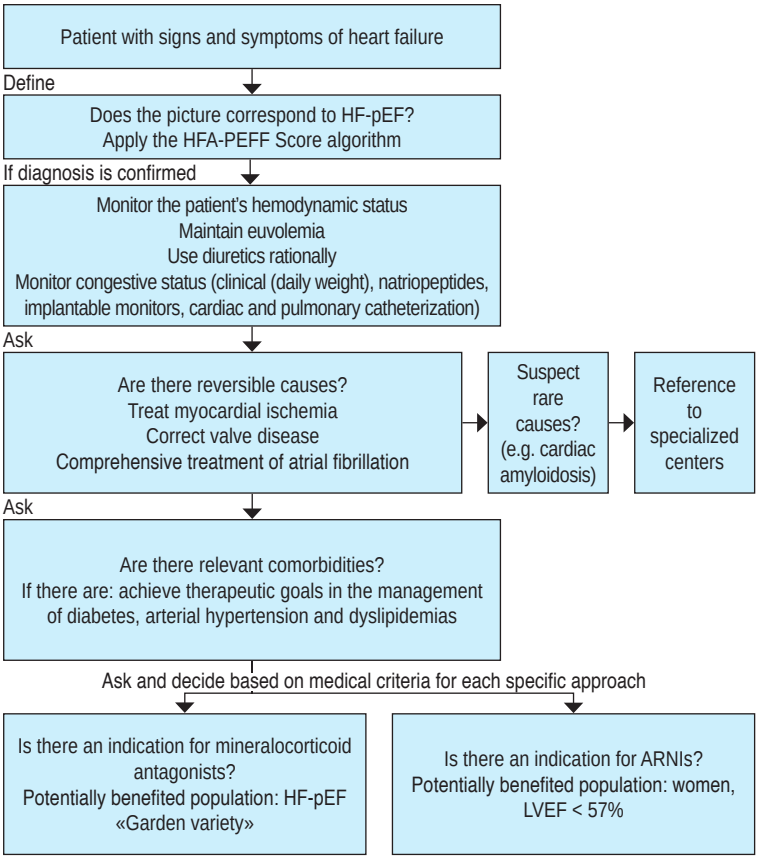


Figure 31: Therapeutic diagnostic approach for heart failure with preserved ejection fraction.
HF-pEF = Heart failure with preserved ejection fraction, HFA-PEFF Score = Heart Failure Association HF-pEF diagnostic algorithm, ARNIs = Angiotensin receptor neprilysin inhibitors, LVEF = left ventricular ejection fraction.

10. Patients with HF-pEF of rare or unknown cause etiologies should be referred to heart failure centers or programs for a specialized approach.

Figure 31 summarizes therapeutic diagnostic approach proposal for HF-pEF.

Finally, it is necessary to promote scientific research in HF-pEF in order to learn more about disease physiopathology and in order to build an optimal treatment for this important group of patients with heart failure.

VII. SPECIAL SITUATIONS: CHAGAS DISEASE, AMYLOIDOSIS, CARDIO-ONCOLOGY, COVID-19

There are clinical scenarios in patients with Heart Failure that are worth noting because they require a specific therapeutic diagnostic approach that goes beyond syndromatic management. Among these we find Chagas disease, amyloidosis, cardiotoxicity from cancer treatments and evidently cardiac involving by SARS-CoV2 virus infection. The following summarizes the points that are considered relevant to consider from this positioning.

1. Chagas disease

110 years after the discovery of Chagas disease, disease physiopathological characteristics affecting different target organs are not fully studied. Undeniably, many cases of ***Chagas disease cause dilated cardiomyopathy*** that leads to heart failure with reduced, often severe, ejection fraction.

In Latin America it is estimated that Chagas disease may cause up to 41% of cases of Heart Failure.[204] In 2015, WHO ranked Mexico as the third country in the world with higher Chagas disease prevalence, only after Argentina and Brazil.[205] Publication considered a potential prevalence of around 876,458 cases, of which 70,117 would have cardiological manifestations corresponding to 8% of the total cases. However, in Mexico there is not a reliable national record of Chagas disease, even though in recent years work has been done to consolidate the data that will allow us to know the epidemiological disease profile. It is therefore ***essential to promote the epidemiological reporting of Chagas disease cases and the creation of a national registry of the Chagas cardiopathy.***

Mechanisms through which Chagas disease leads to myocardial damage are diverse and involve direct myocardial damage by pro-inflammatory cytokines (parasitokines), antibody-mediated damage, micro-circulation alterations, extracellular matrix deformation and alterations in the conduction system.[206,207] Therefore, ***cardiac involvement of Chagas disease not only encompasses heart failure but also numerous electrophysiological manifestations that produce cardiac arrhythmias and conduction disturbances.***

Therefore, Chagas cardiomyopathy is considered to be one of the most difficult and costly causes of heart failure to treat, as it requires not only pharmacological management,

but hospitals and devices with a high level of specialization.[208,209] This is especially important because, to a large extent, those affected by this disease correspond to vulnerable groups belonging to low socioeconomic levels. Hence, ***Chagas disease poses a greater financial risk to health systems.***

Clinically, most patients who reach a structural heart disease start with electrical disturbances, which depend on the time and evolution time of the disease. In most of them, AV conduction blocks or bundle branch blocks are seen, mainly right branch, associated or not with anterior bundle block, without these being the only electrical changes present, since atrial fibrillation can be found too, also manifesting in some cases with embolisms and secondary cerebral vascular event.[210] Regarding the clinical presentation of heart failure, the manifestations do not differ most from those of patients with HF-rEF of different etiology; however, it is common to note that in patients with Chagas HF blood pressure figures are usually lower than in those of different causes. Similarly, chronotropic incompetence has been found to be common in patients with Chagas heart disease and should be considered as an expression of autonomic dysfunction in these patients.[211] In many cases, these situations limit the process of therapeutic optimization especially in terms of the titration of drugs with vasodilator or negative chronotropic potential which are currently considered as the first line in heart failure ma nagement.

In patients with unidentified heart failure, suspected Chagas disease is based on an epidemiological profile and the patient history. It is therefore essential to know if the suspected cases come from endemic areas with high prevalence of the disease in which, additionally, the triatomine is seen. Similarly, patients who have had blood transfusions should be considered, and alternatively those with a suspicious or Mother with Chagas disease diagnose.[212,213]

Confirmatory diagnosis in chronic phase is essentially serological and must be consider using a serological pair simultaneously, a test with high sensitivity (ELISA, using total antigens) with another with high specificity (ELISA, using recombinant antigens).[213] With the use of these two methods diagnostic certainty will range from 98 to 99.5%; serum results with discordant reactivity should be subjected to a third evaluation with another technique (IFI) and if the mismatch is repeated, it would be necessary to re-perform the procedure with a new sample.[213,214]

From a cardiovascular point of view it is essential to have complementary studies to help establish the evolution of the disease and that allow ruling out complications or added comorbidities. Essential studies of a patient with Heart Failure and suspected Chagas Disease include a resting electrocardiogram, radiological chest study, transthoracic echocardiogram and basic laboratories.

Since the disease shows significant involvement of heart structure, an ***echocardiogram represents a critical tool in the diagnostic approach to Chagas heart disease.*** Among the most frequent anomalies are dilation of cavities and alterations in ventricular mobility, initially segmental and characteristically in apical region with or without aneurysm formation; Likewise, the inferobasal and lateral segments are compromised and in advanced stages global alterations of contractility can be identified. Recently Speckle training and Strain techniques are being studied in Chagas heart disease and their usefulness in noninvasive imaging is undeniable. It is noteworthy that the involvement of the right cavities is uncommon, although not impossible, so whenever an echocardiogram is performed on a patient with HF and suspected or confirmed Chagas disease, an assessment of structure and function of right heart should be included.[215]

Cardiac arrhythmias are common in Chagas disease and can even be a direct cause of death in these patients, therefore, the evaluation of rhythm disturbances through studies such as electrocardiographic Holter monitoring is well founded.[216,217]

Once a diagnosis of Chagas disease has been made, it is important to classify patients for the purpose of stratifying risk and defining appropriate treatment. For the classification of chronic chagasic heart disease it is proposed to use the scheme of Latin American guidelines for the management of Chagas disease *(Table 21)*.[217]

The treatment is oriented to the fulfillment of three objectives:

Table 21: Chagas heart disease classification.

Chronic Chagas heart disease					
Acute phase	Chronic phase				
Infected patients with acute manifestations	Chronic without clinical manifestations	Chronic with clinical manifestations			
	A	B1	Dilated Chagas cardiomyopathy		
	Patient at risk of developing cardiac alterations in positive serology	Patient with structural damage, confirmed by electrocardiogram or Echocardiogram without ventricular dysfunction or symptoms of heart failure	B2 Patients with structural damage but no symptoms of heart failure	C Structural damage, ventricular dysfunction, and present or past symptoms of heart failure	D Patients with structural heart damage and severe or refractory symptoms of heart failure

Andrade J[217]

a. **Prevention of triatomid infestation**. It requires a public policy aimed at the elimination of the parasite and its vector. Efforts should be made to increase hygiene and sanitization measures of dwellings in areas of high prevalence. Early recognition of vectors and risks of contagion should also be encouraged so that at-risk people become aware of the scale of the problem and participate in eradication campaigns. In addition, the strengthening of control and safety measures in blood banks and transfusion services in all units of health system in the country should continue and due there is vertical mother-child transmission, it should be encouraged that in those regions of Chagas high prevalence, perinatal care includes suspicion of the disease through medical history and in cases that require it, the intentional search for a potential Chagas infection in pregnant women

b. **Treatment of parasitosis.** The two approved drugs for infection management are Benznidazole and Nifurtimox. Until now, pharmacological treatment with Benznidazole has shown no benefit in patients with established dilated cardiomyopathy, but has shown great benefits in the acute phase, and moderate in the chronic phase without pathology yet demonstrated, just as Nifurtimox, which has not been evaluated in the chronic phase with proven pathology. So its early use in patients with evidence of infection is recommended.[213,214,217,218]

c. **Handling of Chagas heart failure.** Information on the treatment of heart failure in chagas patients has been extrapolated from other studies with non-Chagas pathology, so far the recommendation is to use same principles and measures that have already been described in this document, i.e. the use of ACE inhibitors or angiotensin receptor blockers 2 plus Beta blockers and mineralocorticoid inhibitors as the first line of treatment for neuroendocrine modulation.

However, as mentioned, in a significant number of patients, arterial hypotension or chronotropic incompetence is an obstacle to optimal medical treatment, so special care should be consider in the implementation of therapeutic optimization protocols. In studies such as PARADIGM-HF, a small group of patients with Chagas etiology HF, showed potential benefit from the use of sacubitril-valsartan, which raised the hypothesis of a possible beneficial role of ARNIs in this field; However, until information is available from the clinical studies underway to clarify this point, routine use of ARNIs in Chagas cardiomyopathy management is not recommended as a standard of care, and its use should follow same directions as for heart failure syndrome management. To date, there is insufficient evidence of the use of other drugs to recommend them in this group of patients.[219,220] In patients with Advanced Heart Failure from Chagas cardiomyopathy, cardiac transplantation may be an alternative as long as the criteria for this procedure are met.

Figure 32 summarizes the proposal to address Chagas disease.

In summary, Chagas disease is common in Mexico. Unfortunately ***Chagas cardiomyopathy is an underestimated entity in our environment, therefore it is essential to generate clinical suspicion in patients with a history or high risk profile for Chagas disease.*** Early diagnosis of parasitosis is a window of opportunity to implement antiparasitic treatment. However, in patients with chronic involvement, the usefulness of this management is debatable so all relevant measures for the comprehensive management of heart failure must be implemented.

2. Cardiac amyloidosis

Compared to ischemic heart disease, high blood pressure or diabetes, ***amyloidosis is a rare but important cause of heart failure***.[221]

Amyloidosis is a systemic infiltrative disease that results from the extracellular accumulation of fibrous (amyloid) material in various organs and tissues. It is a genetic disease resulting of chronic inflammation associated with aging.[221,222]

Within the organs frequently affected by amyloidosis is the heart. Patients with cardiac amyloidosis often show structure and function

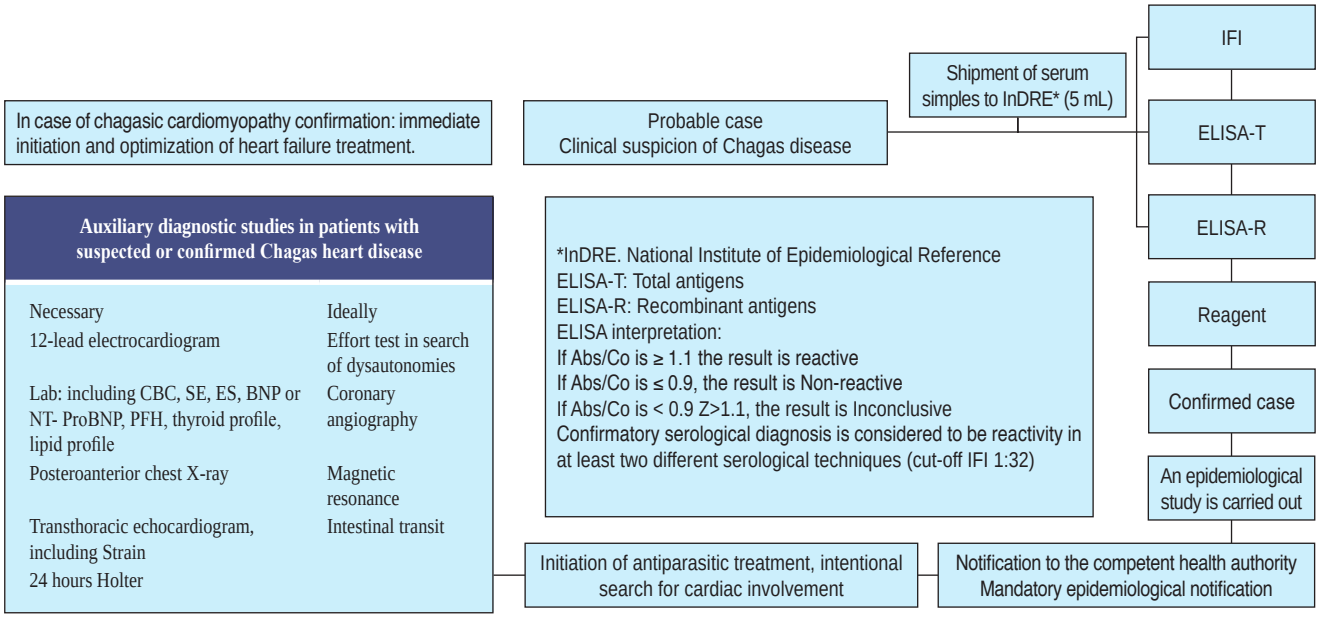


Figure 32: Therapeutic diagnostic approach to the suspicion or confirmation of Chagas disease in Mexico.
CBC = complete blood count, SE = serum electrolytes, BNP = B type Natriuretic Peptide, NT-ProBNP = amino terminal pro B type natriuretic peptide, LFT: liver function tests.

Table 22: Characteristics of the different types of ATTR cardiac amyloidosis.

Variable	ATTRm	ATTR «Wild type»
Gender	Male predominance	Male predominance
Age at presentation	Variable	> 60 years
Cardiac involvement	Variable	Frequent
Extra-cardiac involvement	Dysautonomic symptoms (orthostatism, erectile dysfunction) Polyneuropathy Digestive disorders (chronic diarrhea, constipation) Ocular involvement (glaucoma, intravitreal deposits)	Lumbar canal stenosis Non-traumatic rupture of the biceps tendon Carpal tunnel syndrome
Cardiac alterations	Heart failure Conduction disturbances	Heart failure Conduction disorders Atrial fibrillation Aortic stenosis
Genetic study	Mutation in TTR	Absence of mutations in TTR

alteration in the form of cardiomyopathies resulting in the development of heart failure.

Forms of cardiac amyloidosis may be:[222]

a. Transthyretine amyloidosis (TTRA).
b. Light chain deposit (AL) or primary amyloidosis.
c. Secondary amyloidosis from chronic inflammatory diseases (AA).
d. Other types (amyloid A, apolipoprotein AI, heavy chains and atrial natriuretic peptide).

Among most common types, we find AL amyloidosis where 50% of patients have cardiac involvement with early development of heart failure, these patients are occasionally associated with conditions such as myeloma or lymphoma. The second type in frequency is transthyretine amyloidosis or TTRA, transthyretine is a tetrameric protein produced by the liver. In cases of TTR accumulation amyloidosis we can find a genetic substrate by mutation of protein gene that produces abnormal accumulations of its monomers in different organs and tissues by modifying its molecular structure; similarly we find a wild type (TTRAwt) cause not yet explained and that was formerly associated with patient senescence. *Table 22* summarizes the main characteristics of transthyretin cardiac amyloidosis.[222]

Diagnosis of amyloidosis should always be suspected in patients with heart failure and restrictive cardiomyopathy. Similarly, in patients with myocardial hypertrophy of undetermined origin, the suspicion of amyloidosis should also be established. ***Unfortunately, cardiac amyloidosis represents a challenge for its diagnosis and treatment.***

With regard to diagnosis, different sources report a delay of up to five years from the onset of symptoms.[221,222] Main factors associated with this delay are the lack of knowledge of the disease, the nonspecific clinical presentation, the nihilistic conception of it being a very rare or practically non-existent disease in our setting, considering that there are no effective therapeutic alternatives, or the perception that it is a disease limited to highly specialized centers. For this reason, it is important to change these paradigms and suspect amyloidosis as a cause of heart failure in patients with cardiomyopathies (restrictive or myocardial hypertrophy of unspecific origin), with a family history of amyloidosis or cardiomyopathies and who additionally show alterations in initial diagnostic

aids (electrocardiogram, echocardiogram, biochemical markers). In patients with high suspicion, confirmation is performed through additional studies such as nuclear medicine, cardiac MRI, endomyocardial biopsy, and even a genetic study.[222-224] *Figure 33* summarizes clinical data and paraclinic findings that guide or confirm the diagnosis of cardiac amyloidosis.

Regarding treatment, it is important to note that due to the particular characteristics of these patients, specialized management is required by centers experienced in the management of heart failure. In this regard, ***it is recommended that patients with cardiac amyloidosis be treated in structured programs for the management of heart failure.*** Within general recommendations it is important to maintain euvolemia by individualized fluid consumption and rational use of diuretics to avoid hypotension.[222-225] Beta blockers should be used with great care due to the risk of dysautonomy or heart conduction disturbances. The use of aldosterone renin angiotensin system antagonists is controversial due to the lack of solid data supporting its usefulness in this group of patients; however, in patients with cardiac amyloidosis and HF-rEF, it is reasonable to use it under close medical surveillance particularly in the prevention of arterial hypotension. In patients with atrial fibrillation, the use of oral anticoagulants may be helpful in lowering the risk of thromboembolic complications. Also, in patients at sinus rhythm but severely affected atrial structure and function, the use of oral anticoagulants is reasonable according to the experience of certain specialized centers. The implantation of cardiac electrical stimulation devices is recommended in all patients with indication according to current clinical practice guidelines. Automatic defibrillators may be an option to reduce the risk of sudden death in high-risk patients (ventricular arrhythmias, severe myocardial damage, survivors of a sudden death episode).[222-225] Cardiac transplantation may be considered in patients with advanced HF due to amyloidosis as long as the criteria and requirements for this procedure are met, and the multiorganic involvement and life expectancy of these patients is considered.[224-226] In patients with TTRA amyloidosis, liver transplantation is an option to be considered in conjunction with cardiac transplantation; however, this set of procedures increases the risks of both perioperative and long-term follow-up of patients, so the risk/benefit of patients should always be weighed.

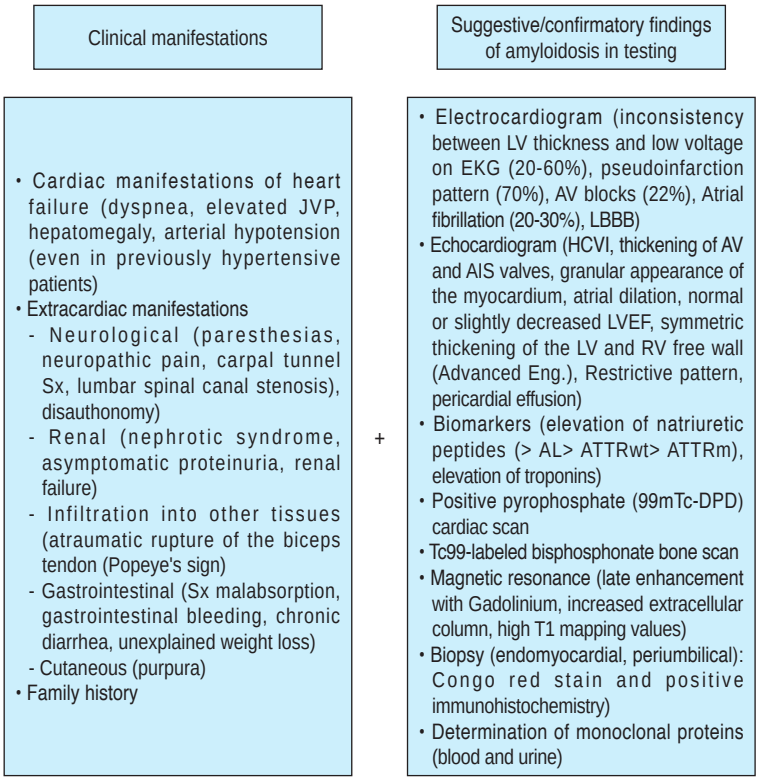


Figure 33: Cardiac amyloidosis diagnosis data guiding.
LBBB = left bundle branch block, AV = atrioventricular valves, LVEF = left ventricular ejection fraction, JVP = jugular venos plethora.

With regard to the specific management of transthyretine amyloidosis, studies with specific drugs have been launched in recent years, either through the suppression of TTR synthesis (Patisiran, Revusiran) or TTR stabilization (Tafamidis) have yielded promising data; however, at this time due to difficulty in access and insufficient long-term evidence, it is difficult to recommend its use as a routine strategy for all cases.[223-225] Therefore, if this possibility is considered, patients should be evaluated individually and always under careful risk/benefit assessment.

In conclusion, ***cardiac amyloidosis is an underestimated clinical entity that requires increasing diagnostic suspicion and confirmation; treatment must be individualized and under a multidisciplinary and high specialty approach.***

Table 23: Immunosuppressive therapy adjustments in heart transplant patients with SARS-CoV-2 infection.

Clinical situation	Action
Mild infection	Maintain regular immunosuppressant treatment or reduce to a lower therapeutic serum level Suspend mycophenolate or azathioprine for 48 hours and reassess initiation
Moderate to severe infection	Consider the suspension of mycophenolic acid/ azathioprine and lowering calcineurin levels Corticosteroid therapy can be increased or even immunoglobulins administered
Pharmacotherapy	There is no specific evidence of any specific pharmacological treatment for SARS-CoV-2 infection, so the care protocols of each center must be followed

Cigarroa LJ et al.[228]

3. COVID-19 and heart failure

COVID-19 pandemic has been the biggest challenge for humanity in the 21st century. With more than 100 million cases and more than 2.3 million deaths as of February 2021, it has become the world's leading public health problem.

SARS-CoV-2 infection often shows extrapulmonary manifestations resulting from each patient's individual inflammatory response as well as direct cellular damage. ***Within the organs affected by COVID-19 there is the heart.***

Cardiovascular manifestations by COVID-19 are diverse and include arrhythmias, exacerbation of chronic myocardial ischemia and of course heart failure.[227]

In regard to COVID-19 and heart failure, it is relevant to consider the following:[227,228]

a. ***Patients with chronic heart failure are not at a higher risk of SARS-CoV2 infection; however, if infected serious complications are more likely to develop.***
b. There is no real evidence that an increase in ACE2 levels is associated with COVID-19 complications. Therefore, ***based on a risk/ benefit analysis it is not recommended to discontinue neurohumoral control management with ACEIs, angiotensin II receptor blockers or ARNIs in patients with chronic heart failure and asymptomatic or non-severe SARS-CoV-2 infection.***
c. ***It is essential to keep chronic HF treatment optimized. Strengthening telemedicine strategies is an option to improve the therapeutic*** adherence of patients with chronic insufficiency and maintain patient monitoring
d. ***In patients with COVID-19 and prior cardiovascular disease, the presence of alert data at cardiovascular level should intentionally be investigated.***
e. ***Biochemical markers such as natriuretic peptides or high-sensitivity troponins may be useful tools for early identification of cardiovascular engagement in patients with COVID-19 even in the absence of symptoms.***
f. Special care should be given to diuretic management and to maintain the ***euvolemic status in patients with COVID-19 and acute heart failure.***
g. Similarly, indiscriminate use of endovenous solutions should be avoided in patients with Heart Failure and COVID-19.
h. ***COVID-19 myocarditis should be suspected in patients with SARS-CoV-2 infection who develop de novo acute HF.***
i. ***Adjustments should be made to immunosuppressive therapy in patients with cardiac transplantation and COVID-19 depending on the severity of SARS-CoV-2 infection*** *(Table 23)*.

The scientific evidence in this area is constantly changing and adjusting so all these recommendations should be taken with reserve of the results of ongoing clinical studies, real-life records and pandemic evolution.

VIII. CARDIO-ONCOLOGY

Malignancies rank third mortality cause in Mexico.[229] Fortunately, great progress has been made in recent decades in terms of decreasing early mortality associated with a significant group of these conditions; however, in cancer survivors, an increase in the frequency of effects of several kinds has been observed, including the development of HF.

The association between cardiovascular effects of cancer therapy is robust. Cardiotoxicity of several used drugs such as chemotherapy as well as radiation therapy increase morbidity and mortality of affected population and this is a topic of greatest relevance in contemporary cardiology. In view of this situation, a new chapter called Cardio Oncology has been opened.

In Heart Failure field, ***chemotherapy cardiotoxicity can develop from asymptomatic left ventricular dysfunction to severe forms of HF.*** The incidence of these events is variable and depends of dose, exposure time, individual patient susceptibility which is associated with idiosyncrasies as well as the existence of preconditions that increase cardiovascular events by themselves (e.g. history of ischemic heart disease, high blood pressure, cardiomyopathies, renal dysfunction). *Tables 24 and 25* show the cardiotoxicity frequency according to the type of medicine and risk factors associated with cardiotoxicity.[230-232]

Table 24: Potential incidence of cardiotoxicity based on anticancer drug type.

Drug	Documented incidence (%)
Anthracyclines (dose-dependent)	
Adriamycin (400-700 mg/m^{2}SC)	3-48
Idarubicin (> 90 mg/m^{2}SC)	5-18
Epirubicin (> 900 mg/m^{2}SC)	0.9-11.4
Antimetabolites	
Clofarabine	27
Monoclonal antibodies	
Trastuzumab	1.7-20
Bevacizumab	1.6-4
Pertuzumab	0.7-1.2
Proteasome inhibitors	
Carfilzomib	11-25
Bortezomib	2-5
Alkylating agents	
Cyclophosphamide	7-28
Antimicrotubules	
Paclitaxel	< 1
Docetaxel	2.3-13
Miscellaneous	
Everolimus	< 1

Modified from: Zamorano JL et al.[230]

Cardiotoxicity manifestations are diverse and include myocardial damage and development of heart failure, development and progression of coronary artery disease, cardiac arrhythmias and thromboembolic events[230-232] *(Table 26)*.

The mechanisms involved in cancer drugs myocardial damage development are multiple and include: endothelial dysfunction, hypercoagulability, direct myocardial damage and increased neuroendocrine over-expression among others.

Therefore, ***it is essential to perform a cardiology evaluation in every cancer patient before, during and that every cancer patient be evaluated for cardiology before, during and after cancer treatment*** in order to prevent, detect and care for the possible chemo or radiation therapy cardiotoxic effects.

Clinical evaluation should include a thorough and accurate medical history by trying to identify those factors or situations that increase the risk of cardiotoxicity. In addition, the rational use of diagnostic aids is essential for early detection and stratification as in many cases the damage is developed and presents even in asymptomatic patients. Within paraclinical studies we have the support of cardiovascular imaging through echocardiography, cardiac MRI, and nuclear medicine. In respect to biochemical markers, natriuretic peptides and high-sensitivity troponins there are two studies that provide the best information regarding hemodynamic behavior and the level of myocardial damage in patients, electrocardiogram is an accessible and valuable tool for timely detection of rhythm and conduction alterations.[230-234] *Figure 34* summarizes general aspects for the diagnostic approach to possible cardiotoxicity from cancer treatments.

Preventing and treating potential cardiotoxic effects of cancer treatment poses a major challenge and requires the integration and intervention of a team that includes oncologists, cardiologists, radio oncologists, internists and related specialists. Therefore, ***it is necessary to promote the creation of cardio-oncology services in Mexico for the prevention, early detection and timely treatment of cardiotoxicity associated with cancer treatments.***

Table 25: Risk factors for cardiotoxicity.

History and previous illnesses	Previous CV diseases
Age: • <18 years and > 50 years (traztuzumab) • 65 years for anthracyclines	Previous heart failure or asymptomatic left ventricular dysfunction
Diabetes	Ischemic heart disease With or without previous heart attacks With or without myocardial revascularization
Chronic kidney damage	Arterial hypertension
Obesity	Cardiomyopathies
Smoking	History of cardiac arrhythmias
Dyslipidemia	Cardiac sarcoidosis
History of radiation therapy	
History of chemotherapy	

Modified from: Zamorano JL et al.[230]

From this consensus, we consider it relevant to take account the following recommendations regarding prevention, early diagnosis and treatment of cardiovascular disorders associated with cancer treatments:

1. The potential risk of cardiotoxicity should be stratified in any patient who is considered to receive chemotherapy or radiation therapy as cancer treatment.[230-232]
2. Medical history should consider the type of cancer, histopathological line, clinical stage, prognosis stratification, proposed cancer plan, cardiovascular history and concomitant treatments
3. Electrocardiogram is mandatory and particularly useful for detecting and monitoring rhythm disturbances and cardiac conduction. The extension of the QTc interval, particularly over 500 msec is associated with the development of severe arrhythmias so the use of medicines that may further prolong this interval should be avoided[230-233]
4. In patients receiving chemotherapy, a LVEF drop of 10% or more from baseline, or LVEF of less than 53% has a potentially treatment cardio toxic effect. If echocardiographic window is unreliable, a three-dimensional echocardiogram or cardiac MRI should be used to accurately define the LVEF and study the ventricular function. Modalities such as Strain may be useful in the study of cardiotoxicity, although there is no consensus on the interpretation of its results[230-234]
5. Elevation of troponins or natriuretic peptides after administration of agents used in chemotherapy is an indication of potential treatment-associated toxicity so this information should be supplemented with cardiovascular imaging studies[230-234]
6. In patients with cancer and previous cardiovascular pathology (e.g. high blood pressure, ischemic heart disease), cardiological treatment must be intensified and control goals ensured in order to reduce the risk of toxic effects of cancer treatment
7. In patients considered with high risk for toxicity associated with cancer treatments, the use of beta blockers, ACE inhibitors, Angiotensin receptor blockers and statins may be a reasonable option for primary prevention of cardiotoxicity events, although their effectiveness is not 100%.[235]
8. Patients who have or develop atrial fibrillation during treatment should receive

anticoagulant therapy as long as there is no formal contraindication for their use.[230-232]

9. Patients with asymptomatic ventricular dysfunction should be considered for treatment with the products listed in subparagraph (g) of this section. In addition, consideration should be given to adjusting the cancer treatment scheme.[230-232]
10. In patients with symptomatic heart failure, the treatment recommended by clinical practice guidelines for the management of heart failure should be instituted. Cancer treatment should be adjusted and in cases of severe HF serious thought must be given to the temporary suspension of the cancer treatment thorough a risk-benefit weighting and under a multidisciplinary approach.[4,230-232]

Figure 35 summarizes measures to consider in the treatment and follow-up of cancer patients and potential risk of cardiotoxicity.

IX. HEART FAILURE CLINICS AND PROGRAMS

All scientific evidence from clinical trials, real-world studies and meta-analysis translates into recommendations embodied in the Clinical Practice Guidelines. Adherence to these recommendations has been shown to improve adverse outcomes in different diseases, particularly heart failure. However, in clinical practice it is not enough to have excellent consensus documents and Clinical Practice Guidelines. So all this evidence and recommendations must be implemented by consolidating heart failure programs and clinics.

Table 26: Cancer drugs cardiotoxic effects.

	Heart failure	Coronary arterial disease	Cardiac arrhythmias	Pulmonary hypertension	Thromboembolic events
Drugs	Anthracyclic Alkylating agents Antimetabolites Antimicrotubules Tyrosine kinase inhibitor Monoclonal antibodies Proteasome inhibitors Everolimus	Fluoropyrimidines Cisplatin Bevacizumab Sunitinib	Bortezimib Cisplatino Doxurubicin Epirubicin Rituximab	Cyclophosphamide Imatinib	VEGF Inhibitors Bevacizumab Sorafenib Sutinib
Manifestations	Functional class deterioration De novo acute HF Chronic decompensated HF	SICAs	Sinus tachycardia AV blocks Atrial fibrillation Ventricular tachycardia Ventricular fibrillation Trosades des pointes Sudden cardiac death	Functional class deterioration	Cerebrovascular events Deep venous thrombosis Pulmonary thromboembolism
Mechanisms involved	Direct myocardial damage Increased neuroendocrine overexpression Fibrosis Hypercoagulability Ischemia	Endothelial damage Hypercoagulability Vasospasm	QT prolongation Electrolyte imbalance Concomitant medications (antiemetics)	Hypercoagulability Endothelial damage	Hypercoagulability

Modified from: Zamorano JL et al.[230]

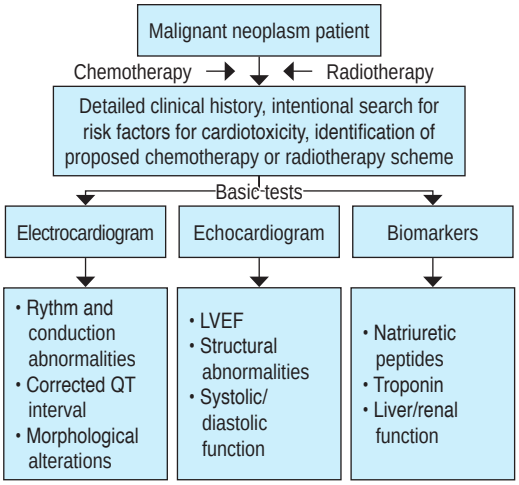


Figure 34: Proposed approach for the detection of cardiovascular effects associated with cancer treatment. LVEF = left ventricular ejection fraction.

Heart failure programs are structured processes that allow the recommendations of the clinical practice guides to be put into operation. These care protocols are designed to identify all actors involved in patient´s care process. They also contain indicators that allow us to evaluate the process and implement continuous improvement actions. For their part, heart failure clinics are structured clinical services or departments whose mission is to implement structured processes for the diagnosis and treatment of heart failure from a multidisciplinary, comprehensive point of view, always focused on patients with heart failure and their direct environment.[236,237]

These clinics started decades ago in our country with the aim of being specialized centers for cardiac transplantation. Currently vision should be expanded to look for a comprehensive syndrome treatment, so it is necessary to define the specific structure and functions of each clinic.

There is no single formula for the creation of heart failure clinics or programs; however, from this positioning we propose to consider the following aspects in the process of designing, implementing and commissioning a heart failure clinic:

1. **Situational diagnosis.** It is necessary to identify heart failure problem in the institution, hospital, clinic or private office in order to know data such as the number of patients, sociodemographic and epidemiological characteristics, hospitalizations frequency, hospital stay time, treatments granted, impact on occupational disabilities and the associated mortality rate. This will allow us to define the magnitude of the problem and direct the clinic or heart failure program to its resolution. In order to develope a situational diagnosis, it is advisable to use basic administration elements such as SWOT analysis and the creation of a risk matrix.
2. **Set objectives and goals.** The objectives and goals of heart failure program or clinic need to be defined clearly, specificly and temporally. Objectives that should not be missed are: patients quality of life improvement, a decrease of hospitalizations due to heart failure decompensation, shortening hospital stay times, the reduction of premature mortality (within the first five years of a heart failure diagnosis), achieving early therapeutic optimization and containment of direct and indirect costs in patient care. As an additional objective it may be considered to promote scientific research in heart failure, training of human resources specialized in heart failure (doctors, nursing, technicians) and knowledge dissemination.[236,238]
3. **Identify the target population.** Based on situational diagnosis and objectives and targets definition, population that will benefit from services portfolio of each specific clinic or heart failure program should be specified. In this regard, it should be defined whether patients at low, moderate or high risk will be accepted depending on the scope of the specific program or clinic. For example, if the program is proposed for a first-level unit of care, it would not be appropriate to consider patients with Heart Failure at high risk of morbidity. For this purpose it is advisable to design a reference and counter-reference criteria scheme, especially if within a health institution with different attention levels that allows to offer services to patients of different risk categories.
4. **Infrastructure.** It is essential to define the basic and expanded elements of infrastructure necessary for the implementation of the heart failure program or clinic. A service of

this nature is often considered to require high-cost inputs, a situation that only applies to centers of excellence or clinics in high-specialty or advanced failure units. However, it should be remembered that one of the purposes of these services is cost containment, so in general terms the following basic elements are required:

a. **For outpatient care:** medical office with dial-up access (ideally internet access) and basic equipment (examination table, scale, meter, sphygmomanometer, pulse oximeter, thermometer), computer equipment, printer. Access to resting electrocardiography and chest radiology studies is desirable. Printed educational material.
b. **For hospital care:** as in subparagraph (a), plus physical space for hospitalization of patients with acute heart failure (in hospitalization floors or critical care rooms), hospitalization beds should have regulatory requirements for health facilities dictated by regulatory authorities such as physical space, access to medicinal gases, monitoring of vital signs, access to red car, among others. In advanced programs it is desirable to have a physical space for the implementation of day hospital programs or infusion centers (see advanced heart failure section). In hospitals, access to emergency services as well as basic cardiological cabinet studies such as echocardiogram, Holter, stress tests and laboratory should be available. In concentration hospitals or high specialty centers, access to hemodynamics laboratory, electrophysiological studies and cardiac surgery will be added.

5. **Personnel:** for the operation of a heart failure program or clinic it is essential to have trained health personnel committed to this service. To do this, it is desirable that human resources receive a specific

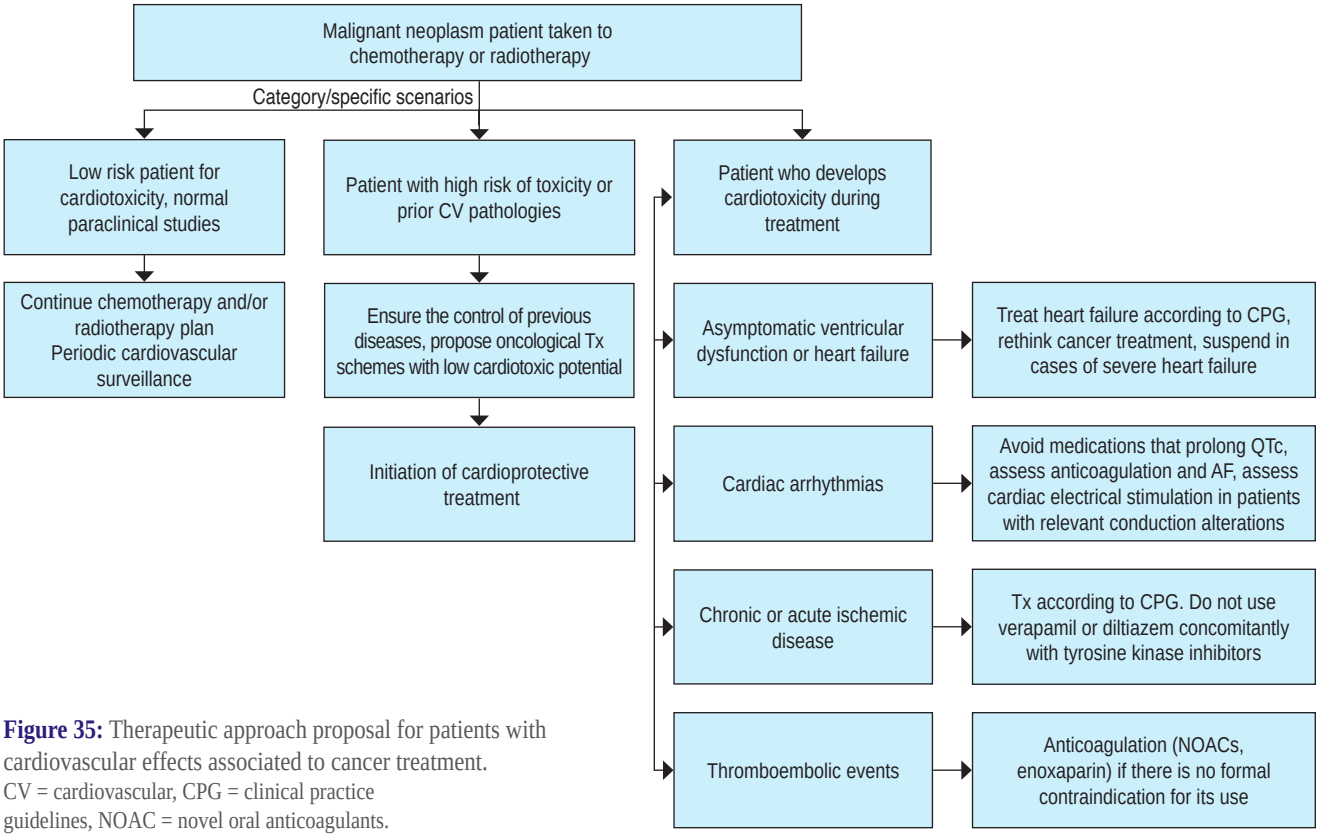


Figure 35: Therapeutic approach proposal for patients with cardiovascular effects associated to cancer treatment.
CV = cardiovascular, CPG = clinical practice guidelines, NOAC = novel oral anticoagulants.

training that allows them to master the professional skills necessary for the conduct of the program. In this sense, there are three categories of staff to drive the clinic or heart failure program:

5.1. **Essential.** There must be at least one cardiologist (or equivalent medical specialist) and one nurse specialized in heart failure. Both will be directly responsible for the program.
5.2. **Extended.** It involves cardiac rehabilitation support, clinical nutrition and psychology specialists as important elements to achieve comprehensive treatment and reintegration of patients to their essential and work activities.
5.3. **Support.** It includes specialists in non-invasive cardiovascular imaging, hemodynamics and interventional cardiology, clinical and interventional electrophysiology, cardiovascular surgery and intensive therapy. They are essential persons in advanced heart failure clinics and programs in centers of excellence or high specialty hospitals since without their participation it would be impossible to implement treatments such as high energy devices, myocardial revascularization, mechanical circulation assistance, and cardiac transplantation among others.

6. **Engineering and work plan.** Once the above points have been defined, it is essential to generate a work plan that specifies the model of the clinic or program, the definition of the portfolio of services and the reference and counter-reference criteria already indicated. There are different models of Heart Failure Clinic and each institution, hospital or practice will define according to its situational diagnosis and perspectives the one that best suits their needs and objectives. What needs to be highlighted, however, is that in any case the programmes should always be focused on the patient and their social and family environment and should be advocated for multidisciplinary models that expand the medical-patient binomial relationship to an expanded scheme where heart failure nursing plays a key role.
7. **Care protocols.** Once the program or clinic model is defined in the overall work plan, a specific care protocol should be built. This document should make clear the steps to be taken since the generation of diagnostic suspicion, confirmation of diagnosis, classification and stratification methods and scales, components of non-pharmacological, pharmacological and invasive treatment, as well as the specific responsibilities of each of the actors involved in the process. The purpose of the care protocol is to standardize specific criteria and actions in order to increase opportunity in care, resource efficiency and improve outcomes. These standardized processes have proven useful in all the centers that have implemented them, and as additional data they allow cost containments by making a more rational use of human resources and patient care materials.
8. **Database registry systems.** It is important to emphasize the importance of measuring and recording processes in health care and administration in general. The phrase «What is not measured cannot be improved» makes the greatest sense in terms of the implementation of a clinic or heart failure program. So it is necessary to implement a patient registration system that allows to know the day-to-day operation, the characteristics and the results of the implementation of the care protocols. This is not only an administrative tool that will identify areas of improvement, but is a fundamental tool for health research. Since this process involves the use of sensitive data, it is important that the records have all provisions stated by legislation and regulations regarding registration systems and databases.
9. **Continuous control and improvement.** Within a comprehensive Work Programme it is necessary to develop process indicators that allow, from an objective point of view, to identify in a timely manner the efficiency of processes as well as areas of opportunity

that are capable of improvement. Key indicators are the overall, cardiovascular and heart failure mortality rate, the rate of early reinstatements due to heart failure decompensation, the percentage of patients with optimized treatment, the percentage of response to cardiac resynchronization therapy, the short-, medium- and long-term survival rate in transplanted heart patients, among others.

10. **Nursing in heart failure**. ***The role of nursing in a clinic or heart failure program is fundamental,*** such a service may not be conceived without the participation of nursing professionals. Essential nursing work includes:[239,240]

    10.1. **Patient identification.** Nurses are able to make an early examination of patients with heart failure syndrome who are in clinical departments outside the heart failure program and therefore suggest the reference to the specialized service.

    10.2. **Clinical evaluation and patient environment.** Process systematization allows nursing personnel in many cases to be the first contact with patients and according to structured medical history, to emphasize the importance of this document as a starting point for comprehensive patient evaluation and diagnostic approach.

    10.3. **Conducting the nursing process.** The activities of the nurse process such as drug drugs administration or hospital registration, and care are of better quality when performed by staff trained in heart failure since the professional skills developed allow you to recognize early alarm data as well as advances in treatments.

    10.4. **Evaluation in the pre-discharge period.** As noted, the vulnerable period of heart failure is the best time to initiate or optimize a disease-modifying treatment. The use of checklists in pre-discharge patients is a safety barrier to confirm that all patients who are discharged after hospitalization for acute heart failure have their basic medicines and educational measures to move to the chronic phase of the disease in a safe framework. The use of these checklists by nurses are a key part of the therapeutic optimization protocols.

    10.5. **Patient collection data.** Nursing involvement in the systematized and prospective registration of patients in a clinic or heart failure program is crucial as it meets the dual objective of both information and in-depth understanding of their target population characteristics to strenghten their involvement in the monitoring processes.

    10.6. **Patient monitoring.** Monitoring patients beyond scheduled appointments or cardiac failure decompensation hospital stays is critical in any structured heart failure program. This process that may be face-to-face or remotely (telephone, video calling platforms), it allows to improve therapeutic adherence, strengthen the link of patients with their service providers, and recognize early alert data that are susceptible to receive additional treatments immediately. This process has become particularly indispensable during the COVID-19 pandemic where it is important that this vulnerable population does not suspend their medical care.

    10.7. **Education.** Patient, family members and caregivers education, is essential in order to achieve their empowerment and improve adherence to therapeutic measures and recognition of warning signs. Without a targeted medical education process, the affected population becomes more vulnerable, while a population that masters basic and expanded knowledge of their condition is able to improve care processes outcome. Nursing participation is crucial due to their training, assertive communication skills, and knowledge of cases beyond the biological sphere, as

they are responsible for the heart failure nursing programs, they become the ideal personnel to conduct this process.

Figure 36 summarizes the components and steps to be follow for the creation of clinics and heart failure programs.

Worldwide, implementation of structured heart failure management clinics and programs has consistently demonstrated improving health care outcomes and containing healthcare costs.[240] Unfortunately, in Mexico the coverage of these services is still scarce so from this positioning it is considered essential to encourage the creation of structured ***clinics and programs for HF management in the three health system care levels***.

X. HEART FAILURE RESEARCH

Medicine is an activity that is constantly changing and evolving. Research is the engine that allows the development of this discipline and in particular improves outcomes derived from the medical act.

As heart failure is one of the most relevant problems in contemporary cardiovascular medicine, in recent years it has been the focus of multiple clinical trials, meta-analysis, prospective studies and real-world evidence. All of this has impacted the creation of consensus documents, clinical practice guidelines and discussions on how best to treat patients.

Unfortunately, Mexico has had little involvement in cardiac failure research, so from this positioning ***it is considered necessary to develop and promote HF research in all its modalities in our country.***

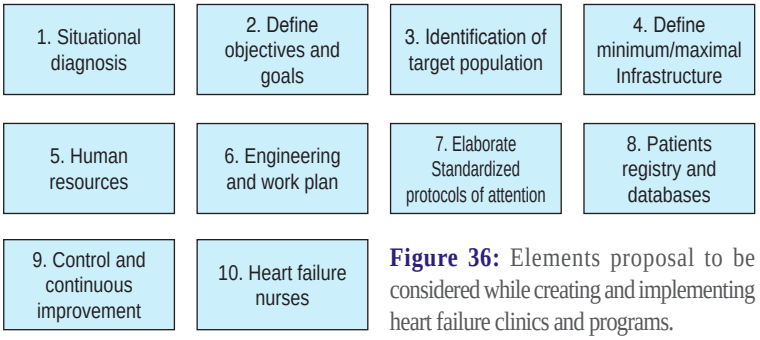


Figure 36: Elements proposal to be considered while creating and implementing heart failure clinics and programs.

The above in order to better understand our national environment, but also to be protagonists in global concert of scientific evidence, and to transform our reality from an information consumption economy to a model that generates scientific evidence.

To achieve this, it is recommended that those in charge of heart failure programs have professional skills for the performance and conduct of research projects. It is also necessary to strengthen the inclusion of research programs, particularly those with a translational approach within the curriculum of medical, nursing and medical specialties, to allow an objective and prompt improvement of medical actions at all levels.

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Disponible en presentaciones que facilitan el proceso de titulación de dosis

Dosis

Iniciar con: **3.125 mg** c/12 h, durante 2 semanas

Si es tolerado, incrementar a **6.25 mg** c/12 h, en intervalos no <2 semanas

Posteriormente: **12.5 mg** c/12 h

Finalmente: **25 mg** c/12 h

La dosis deberá incrementarse hasta el nivel máximo tolerado (**Dosis máxima** para todo paciente con ICC y peso corporal de hasta 85 kg, en pacientes de >85 kg, la dosis máxima recomendada es de 50 mg c/12 h)

Clave Cuadro Básico 2545

Información para prescribir. Dilatrend® (carvedilol) tabletas.
Reg. No. 034M92 SSA IV. Material exclusivo para el profesional de la salud. No. de Aviso de Publicidad: 203300202C4035.

Línea Cardiovascular m8

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