

## Editorial

# Comments on the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure



Comentarios a la guía ESC 2016 sobre el diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica

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## INTRODUCTION

In accordance with the policy on clinical practice guidelines established by the Executive Committee of the Spanish Society of Cardiology,<sup>1</sup> the current article discusses the most notable and novel aspects of the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure (HF).<sup>2</sup> The aim of the guidelines is to update our knowledge of the diagnosis and treatment of HF based on the best clinical evidence available.

## CRITICAL EVALUATION OF SALIENT AND NOVEL CONTRIBUTIONS

The most important developments are listed in [Table 1](#).

## DEFINITION, EPIDEMIOLOGY, AND PROGNOSIS

Although the clinical definition of HF based on the presence of specific symptoms and signs is unchanged, the guidelines stress the importance of HF detection and diagnosis in the asymptomatic or largely symptomless phase because appropriate therapy can reduce disease progression and mortality.

The main development is undoubtedly the introduction of the concept of HF with mid-range ejection fraction (EF) (HFmrEF). This new entity, placed between the well-established HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF), occupies the gray area of individuals with an EF between 40% and 49%. According to the authors, the demarcation of this group and its identification in the clinic should help to promote research into the underlying causes of HF in this type of patient, improve our understanding of its

pathophysiology, and intensify the search for better treatment strategies. However, this classification appears arbitrary and, thus far, lacks clinical significance.

Data on HF epidemiology and hospitalization indicate the decreased incidence of HFrEF and the parallel increased incidence of patients with HFpEF. The latter phenomenon is mainly due to the following underlying risk factors: population aging and weight gain, greater detection of HF in women, and increased hypertension prevalence.

## DIAGNOSIS

Because the diagnostic suspicion relies on symptoms and signs of congestion, medical history and physical examination continue to be vital for the syndromic diagnosis of HF. The document presents an interesting table aimed at physicians attending non-acute patients. This table summarizes both the most typical and less frequent signs and symptoms of HF, which should be known by all physicians. Three complementary pillars of the syndromic diagnosis of HF now supplement medical history: electrocardiography (ECG), determination of natriuretic peptide levels, and echocardiography. The use and systematic application of these methods are well demonstrated in a new diagnostic algorithm. This algorithm places special emphasis on the use of echocardiography to differentiate HFrEF, HFmrEF, and HFpEF. Particular attention is paid to the diagnosis of this last entity because it is the most common form of HF in elderly patients with multiple comorbidities and has a poorly defined therapeutic behavior. The diagnosis of HFpEF requires all of the following:

- Presence of symptoms and signs of HF.
- EF  $\geq$  50% (40%–49% for HFmrEF).
- Elevated levels of B-type natriuretic peptide (BNP) ( $>$  35 pg/mL) or N-terminal pro-B-type natriuretic peptide (NTproBNP) ( $>$  125 pg/ml).
- Objective echocardiographic evidence of other cardiac functional (E/e' ratio) or structural (left ventricular hypertrophy, left atrial volume) alterations.

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**Table 1**  
The Most Novel Contributions

1.	New EF-related classification of HF with the introduction of a third type called HF with mid-range EF (HFmrEF) for patients with an EF of 40%-49%
2.	New diagnostic algorithm for chronic HF based on the systematic evaluation of patients' clinical history, natriuretic peptides, and echocardiography
3.	Recommended for the first time the use of a new dual inhibitor of neprilysin and angiotensin receptors (sacubitril/valsartan) (class I, level of evidence B)
4.	Recommendation for ivabradine in patients with HF and reduced EF (HFrEF) who are still symptomatic despite OMT, in sinus rhythm, and with a HR $\geq$ 70 bpm to reduce clinical events (class IIa, level of evidence B; class IIa, level of evidence C in patients with beta-blocker intolerance)
5.	In patients with ACEI and ARB intolerance, recommendation for combined hydralazine and nitrates to reduce the risk of death (class IIb, level of evidence B)
6.	CRT implantation is contraindicated when the QRS duration is $<$ 130 ms and its indication is strengthened when the duration is $>$ 150 ms with LBBB morphology (class I, level of evidence A) or 130-149 ms (with LBBB: class I, level of evidence B; with other morphologies: class IIb, level of evidence B)
7.	ICD therapy is not recommended in patients with AMI and HF during the first 40 days (class III, level of evidence A) or for patients in NYHA IV; a wearable defibrillator may be considered as bridging therapy for patients at risk of sudden cardiac death (class IIb, level of evidence C)
8.	Introduction of the concept of "early initiation" of appropriate therapy in acute HF. New algorithm for the combined diagnosis and treatment of acute HF according to the presence or absence of signs or symptoms of congestion or hypoperfusion
9.	Recommendation to determine natriuretic peptide levels in all patients with acute dyspnea and suspected acute HF (class I, level of evidence A)
10.	Change in the strength of recommendation for circulatory support devices
11.	Application of HF prevention strategies: OMT of cardiovascular risk factors and use of ACEIs and beta-blockers for patients with asymptomatic left ventricular dysfunction and history of AMI

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; bpm, beats per minute; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; OMT, optimal medical therapy.

For the first time, the definition of HFrEF and HFmrEF requires the presence of elevated levels of natriuretic peptides, reflecting the importance of these proteins as a diagnostic tool in HF.

An important aspect mentioned in the guidelines is the difficulty of HF diagnosis in patients with atrial fibrillation (AF), particularly in terms of BNP and NTproBNP levels, because the cutoff levels for these peptides should be higher in patients with this condition.

## CARDIAC IMAGING

Imaging tests should only be performed when deemed necessary for diagnosis or treatment. For example, a simple chest X-ray is useful in the emergency department but is of little to no use in non-acute patients.

As mentioned above, echocardiography is the method of choice for determining systolic and diastolic function in patients with HF.

Cardiac magnetic resonance is recognized as the gold standard for the evaluation of the volume, mass, and EF of both ventricles. It is the leading alternative to echocardiography (particularly for imaging the right ventricle) and the method of choice for patients with complex congenital heart disease. It is the best imaging method to detect myocardial fibrosis and for the diagnosis of amyloidosis, sarcoidosis, hemochromatosis, Chagas disease, and Fabry disease.

Single-photon emission computed tomography (SPECT), positron emission tomography (PET), and noninvasive coronary angiography with multidetector computed tomography (MDCT) can be useful in specific situations. Notably, most of these recommendations, even the class I recommendations, have a level of evidence of C.

## POSSIBILITY OF PREVENTING OR DELAYING THE DEVELOPMENT OF CLINICAL HF OR PREVENTING DEATH DUE TO HEART FAILURE BEFORE THE ONSET OF SYMPTOMS

This section considers the evidence available on a fact well proven in clinical trials: control of HF risk factors can delay or even stop the natural course of the disease. The recommendations table in this section shows a list of available strategies for the primary prevention

of HF involving the general systematic control of risk factors by both pharmacological and nonpharmacological approaches. The most relevant innovation in this section is that the new inhibitors of the renal tubule sodium-glucose cotransporter should be considered in the treatment of diabetes mellitus to prevent or delay HF development and reduce mortality (class IIa, level of evidence B).

## PHARMACOLOGICAL THERAPY

Pharmacological treatment of HF is a field undergoing continuous development and is the main reason for the improved prognosis and quality of life of patients. However, there are priority research needs for acute HF, HFpEF, and HFmrEF.

### Basic Considerations for the Pharmacological Treatment of Heart Failure

Special emphasis is given to the need to use drugs with proven prognostic benefit—the pillars of optimal medical therapy (OMT)—at the recommended dosages, because this aspect is an area with considerable room for improvement in patients in the real-world setting.

### Comments on the Proposed Drug Selection Algorithm for heart failure with mid-range ejection fraction

The guidelines strengthen the recommendation for the use of angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) due to robust evidence showing that these drugs improve survival and reduce the risk of HF hospitalization. Again, angiotensin receptor blockers (ARBs) are relegated to an alternative to ACEIs in patients with ACEI intolerance. It might be surprising that only beta-blockers, MRAs, and sacubitril/valsartan are recommended to reduce the risk of sudden cardiac death in patients with ventricular tachyarrhythmias. This recommendation is based on the beneficial mortality results of the major clinical trials of these compounds, findings not obtained

with ACEIs or ARBs. In this case, analysis of a nonprimary outcome has led to the strongest recommendation possible (class I, level of evidence A).

The controversy surrounding the effectiveness of beta-blockers in patients with chronic HF deserves special mention. In a recent metaanalysis of the results of the major clinical trials involving these drugs, there was no benefit in terms of a reduced need for hospitalization or mortality.<sup>3</sup> However, this analysis was from a retrospective study based exclusively on the analysis of patient subgroups and no clinical trial has specifically explored this hypothesis. Another recent metaanalysis of patients in sinus rhythm found a significant prognostic benefit, including reduced overall mortality, independent of age and sex.<sup>4</sup>

The use of MRAs in patients with chronic HF requires the patient to be symptomatic despite OMT with diuretics, ACEIs, and beta-blockers. This recommendation is based on the designs of the clinical trials of these compounds that included symptomatic patients (New York Heart Association [NYHA] class II-III). However, in clinical practice, application of this recommendation to patients with HF<sub>rEF</sub> is difficult because these drugs are typically recommended from initial diagnosis due to their consistently proven clinical and prognostic value.

Surprisingly, the algorithm summarizing the therapeutic recommendations after MRA treatment for patients with HF<sub>rEF</sub> appears to assign equal strength to cardiac resynchronization therapy (CRT) and ivabradine. However, the algorithm tries to reflect the different magnitudes of benefit by using color coding for the distinct levels of evidence.

## I<sub>r</sub> Current Inhibitors

There are subtle changes from the previous guidelines in the recommended use of ivabradine. The recommendations of the current guidelines (class IIa, level of evidence B) focus on patients hospitalized in the previous year, with OMT but still symptomatic, in sinus rhythm, and with a heart rate (HR)  $\geq$  70 bpm, because ivabradine reduces the combined risk of hospitalization and cardiovascular death (the primary outcome of the pivotal study). This recommendation differs from those of previous guidelines, which considered only the reduced need for hospitalizations, because this was the component showing a significant benefit; however, it is unusual to individualize the components of the primary outcome of a clinical trial to establish the recommendations for the clinical use of a drug. In addition, and as mentioned in the guidelines, the European Medicines Agency, based on a retrospective analysis requested by the agency, recommend the use of ivabradine in this setting in patients with a HR > 75 bpm because both components of the primary outcome of the SHIFT study showed a significant reduction. There is also an improvement in the strength of the recommendation for the use of ivabradine in patients with contraindication or intolerance to beta-blockers (class IIa, level of evidence C). A recent Spanish study is worth mentioning because it showed the usefulness of this compound in hospitalized patients, with a greater reduction in HR without adverse effects, although in a relatively small number of patients.<sup>5</sup>

## Angiotensin Receptor Neprilysin Inhibitor and Angiotensin Receptor Blocker

The main therapeutic innovation in the guidelines is the inclusion of a new class of drugs, angiotensin receptor neprilysin inhibitors (ARNIs), in place of ACEIs or ARBs in the therapeutic strategy for patients with HF<sub>rEF</sub>.

The first compound from this drug family, LCZ696, combines valsartan and sacubitril (a neprilysin inhibitor) in a single molecule. This compound limits the degradation of natriuretic peptides, bradykinin, and other vasoactive peptides that provoke diuresis

and natriuresis, block myocardial cell proliferation, and favor myocardial relaxation. In addition, the increased bioavailability of natriuretic peptides inhibits activation of the renin-angiotensin-aldosterone system. Selective blockage of the angiotensin II receptor AT1 by valsartan is associated with vasodilation, diuresis, and natriuresis and limits cardiac hypertrophy. A recent publication from a Spanish group<sup>6</sup> stressed the relationship between plasma neprilysin activity and prognosis in patients with HF<sub>rEF</sub>, pathophysiological evidence strengthening the value of this component as a therapeutic target.

Thus, it can be considered a 2-pronged drug because it would both potentiate defense mechanisms against cardiovascular disease and limit the activity of deleterious systems.

The guidelines summarize the results of the PARADIGM-HF clinical trial. This study analyzed the effectiveness and tolerability of LCZ696 in stable ambulatory patients with HF<sub>rEF</sub> (LVEF < 40%, changed to < 35% during the study) under ACEI treatment and without severe deterioration in renal function (estimated glomerular filtration rate > 30 mL/min/1.73 m<sup>2</sup>).<sup>7</sup> Special mention is required of the strength and homogeneity of the clinical benefit and prognosis in all components analyzed, in line with that observed for the primary endpoint as well in the different subgroup analyses. As insisted in the guidelines, physicians should strictly adhere to the selection criteria for patients before beginning treatment with a compound included for the first time in clinical guidelines and without extensive experience in standard clinical practice.

Accordingly, there are some noteworthy possible adverse effects and precautions. Before LCZ696 treatment is begun, ACEI treatment should be withheld for at least 36 hours and there should be a period of dose adjustment with the new drug; LCZ696 should never be combined with an ACEI or ARB, as also noted in a recent American consensus document.<sup>8</sup> A recent publication analyzed the tolerability of the initiation/uptitration of LCZ696 from 50 to 200 mg/12 hours over 3 or 6 weeks and found a similar tolerability profile to that of other drugs used for HF<sub>rEF</sub>. However, dose adjustment over the longer period enabled a greater proportion of patients in the low-dose ACEI/ARB group before the change to achieve the target dose.<sup>9</sup> This aspect is especially relevant given the higher frequency of symptomatic hypotension in the LCZ696 group.

## Comments on the Therapeutic Options Considered To Have Lower Levels of Evidence

The recommendation is maintained for the use of the combination of hydralazine and isosorbide dinitrate in black patients with advanced HF<sub>rEF</sub> (NYHA III-IV) despite OMT.

Some controversy continues to surround long-term digoxin therapy and these guidelines limit its clinical use to patients in sinus rhythm who are still symptomatic despite OMT.

The selection of antidiabetic drugs for patients with HF deserves a mention due to the prevalence of the association and after the publication of the EMPA-REG OUTCOME<sup>10</sup> (empagliflozin) and LEADER<sup>11</sup> (liraglutide) studies. Although the proportion of patients with clinical HF was small in both studies (specifically, the LEADER study allowed the inclusion of patients in NYHA II-III), the reduction in cardiovascular complications seen with both compounds and, particularly, the reduced incidence of clinical diagnosis of HF in the EMPA-REG study have led to empagliflozin being recommended as a drug for disease prevention in diabetic patients. In addition, the neutral effect seen in the LEADER study could also indicate a possible role for the drug in the treatment of diabetic patients with HF. However, given that the evidence for SGLT2 inhibitors is limited to a single study, the current recommendation for diabetic patients with HF is that metformin should be considered as the first-line drug (class IIa, level of evidence C), except when the patient has severe renal or liver failure.

## Comments on the Treatment of heart failure with preserved ejection fraction and reduced ejection fraction

Despite the limited understanding of the clinical characteristics and prognosis of the HFmrEF group, the guidelines include both groups of patients in the same section, bearing in mind that they were included in the clinical trials of patients with HFpEF. In absence of significant developments in this area, with the results of the published clinical trials failing to find significant prognostic benefit from any of the tested drugs, the guidelines insist on the appropriate phenotypic characterization of this type of patients with a therapeutic approach aimed at limiting the impact of comorbidities, preventing factors that precipitate clinical destabilization, and cautiously using diuretics to limit congestion.

### ELECTRICAL THERAPY: IMPLANTABLE CARIOVERTER-DEFIBRILLATORS AND RESYNCHRONIZATION THERAPY

The CRT recommendations have been updated for patients with LVEF  $\leq$  35% who are symptomatic despite OMT and in sinus rhythm, without any differentiation according to their NYHA function class (II-IV). Cardiac resynchronization therapy is not recommended in patients with a QRS duration  $<$  130 ms (class III, level of evidence A) and, conversely, is indicated for patients with complete left bundle branch block (LBBB) and a QRS duration  $\geq$  130 ms. If the patient has LBBB and QRS  $>$  150 ms, the recommendation is class I, level of evidence A, whereas the recommendation becomes class I, level of evidence B if the QRS is between 130 and 149 ms. It is difficult to explain why a class I recommendation has been maintained for a QRS between 130 and 149 ms because both subgroup analyses of the large CRT studies and the 2 metaanalyses mentioned in the guidelines as the basis for this indication show no survival benefit in patients in this range of QRS duration.

In the current American guidelines from the ACC/AHA, this approach received a type IIa recommendation in this population.<sup>12</sup>

If there is no LBBB, CRT should be considered for patients with QRS  $\geq$  150 ms (class IIa, level of evidence B), with a more limited indication (class IIb, level of evidence B) for a QRS duration from 130 to 149 ms. Thus, the guidelines reflect the validity of the ongoing controversy regarding whether the indication for CRT should be based only on the duration of QRS or whether it should include its morphology.

For patients with AF and HFpEF (EF  $<$  35%), in NYHA III-IV despite OMT, and with QRS  $>$  130 ms, CRT should be considered if it can achieve close to 100% biventricular capture (class IIa, level of evidence B). Implantation of a CRT device is also recommended if a pacemaker is indicated due to heart block, independent of baseline rhythm (class I, level of evidence A).

Implantable cardioverter-defibrillators (ICDs) are indicated for secondary prevention in patients with an estimated survival less than 1 year (class I, level of evidence A). The guidelines recommend with a class I indication their use for primary prevention in patients with HF and reduced systolic function (EF  $<$  35%) despite OMT (3 months) who are in functional class II-III. However, different levels of evidence are recognized in patients with ischemic cardiomyopathy (level of evidence A) vs nonischemic dilated cardiomyopathy (level of evidence B). The recent release of the results of the DANISH study,<sup>13</sup> subsequent to the publication of these guidelines, will mean a drastic change in the indication for ICDs in patients with nonischemic cardiomyopathy: this randomized trial, whose primary endpoint was mortality, showed no benefit from ICD implantation in this patient group (although subgroups of patients  $<$  59 years do appear to benefit). Thus, the use of ICD for primary prevention in nonischemic cardiomyopathy would be relegated to select individuals, more in accordance with a class IIb indication.

## ACUTE HEART FAILURE

The guidelines expand the section dedicated to acute HF (AHF) compared with the previous edition. Its initial characterization can be performed using the Nohria classification. This system is based on the presence or absence of signs or symptoms of congestion—pulmonary or systemic—(patients “wet” or “dry”) and peripheral hypoperfusion (patients “cold” or “warm”). These categories are combined to give 4 clinical profiles used to outline the initial drug therapy.

The pillars of the initial diagnosis continue to be medical history and physical examination, together with a series of additional tests—chest X-ray, ECG (due to its very high negative predictive value), and laboratory variables (all class I, level of evidence C).<sup>14</sup> Determination of natriuretic peptide levels is recommended in all patients with acute dyspnea and suspected AHF<sup>15</sup> (class I, level of evidence A). In this case, the cutoff points are higher for the diagnosis of AHF than for the diagnosis of chronic HF. Echocardiography is recommended in the first 48 hours but should be performed immediately in patients with hemodynamic instability or suspected life-threatening conditions (class I, level of evidence C).

Immediate care is based on noninvasive monitoring of blood pressure (BP), HR (ECG), and oxygenation (pulse oximetry) (all class I, level of evidence C). Invasive monitoring using pulmonary artery catheterization may be considered for patients with symptoms refractory to therapy, above all if they have hypotension with hypoperfusion (class IIb, level of evidence C). Patients with AHF should ideally be transferred to hospitals with a cardiology service and coronary or intensive care unit. Patients with respiratory failure or hemodynamic instability should be transferred to facilities able to provide respiratory and cardiocirculatory support and specific therapy should be started as soon as possible (class IIa, level of evidence B).

After the initial evaluation and stabilization, the guidelines recommend subsequent identification of the potential causative or precipitating factors of the decompensation. For this purpose, the use is recommended of the mnemonic rule CHAMP (corresponding to the initials of acute Coronary syndrome, Hypertension emergency, Arrhythmia, acute Mechanical cause, and Pulmonary embolism) to direct patients with a diagnosis to undergo immediate specific treatment or otherwise initiate the diagnostic work-up and general treatment.

The initial treatment guidelines include the recommendation to avoid oxygen supplementation in normoxic patients (class I, level of evidence C) and the performance of arterial blood gas in patients with pulmonary edema and COPD (class IIa, level of evidence B). Noninvasive ventilation (class IIa, level of evidence B) should be considered from the beginning for patients with respiratory failure, whereas intubation is to be reserved for patients with persistent respiratory failure (class I, level of evidence C). The use of morphine or opiates is more restricted than in previous guidelines; their systematic use is not recommended but they can be specifically considered to alleviate dyspnea and anxiety in acutely dyspneic patients (class IIb, level of evidence B).

The guidelines recommend the identification and prioritization of the remaining drug therapy based on the characterization of the initial clinical-hemodynamic profile of the patient. Most patients have symptomatic HF and treatment involves the use of diuretics to alleviate the congestion, as well as vasodilators in patients with a suitable BP. Intravenous loop diuretics are indicated to reduce congestion and alleviate symptoms in all of the above patients (class I, level of evidence C). The initial dose should be the lowest that has the desired clinical effect, beginning with 20-40 mg furosemide i.v. (or equivalent) for patients with *de novo* AHF or chronic HF without previous diuretic treatment and at least the equivalent of the oral dose in those on long-term diuretic therapy (class I, level of evidence B), whether via bolus or perfusion (class I, level of evidence B).

Vasodilator therapy (nitrates, sodium nitroprusside, nesiritide) should be considered for all patients with AHF and systolic BP > 90 mmHg (class IIa, level of evidence B) and as primary therapy in patients with hypertensive AHF (class IIa, level of evidence B), in conjunction with blood pressure monitoring if intravenously administered. Patients with cardiogenic shock should be treated with inotropic agents and, when necessary, vasopressors. Mechanical circulatory support should be considered in patients with refractory disease.

When permitted by the hemodynamic conditions and contraindication status of the patient, chronic treatment that modifies the HF course (ACEIs, beta-blockers, and MRAs) should be continued in patients already receiving them (class I, level of evidence C).

The criteria for hospital discharge are clinical and hemodynamic stability, including normovolemia obtained with evidence-based treatment, stable renal function for at least 24 hours prior to discharge, and receipt of education focused on self-care advice. The other key aspect is follow-up during the high-risk phase. Ideally, the management process will include patients in management and follow-up programs before their discharge and involve coordination with the primary care team, with check-ups by a general practitioner in the first week and by a cardiologist linked to the hospital within 2 weeks after discharge. Patients with chronic HF should undergo follow-up with a multidisciplinary team.

### MECHANICAL CIRCULATORY SUPPORT AND HEART TRANSPLANT

The guidelines present various novel aspects related to mechanical circulatory support (MCS) that will be useful in clinical practice.

In the first place, the INTERMACS scale is included as a table. Using this table, as an aid to decision-making, the survival of stages IV ambulatory (INTERMACS 4 and 5) can be compared with the survival estimated via the different risk scores.

Similarly, the guidelines mention the SAVE (Survival After Venous-arterial Extracorporeal Membrane Oxygenation [ECMO]) risk score, which can help to calculate expected survival in patients receiving ECMO for refractory cardiogenic shock.

Another considerably useful aspect is the inclusion of eligibility criteria for implantation of a left MCS. These criteria reveal a development, namely, MCS contraindication due to the presence of combined severe right ventricular dysfunction and severe tricuspid regurgitation. A noteworthy aspect is the replacement of the MCS recommendation as “bridge to heart transplantation” (class I, level of evidence B) by the indication “bridge to transplant indication” (class IIa, level of evidence C). We agree that the scientific literature is yet to prove a universal benefit of MCS in patients on the transplant waiting list, but the cumulative experience with these devices in this setting reveals excellent results. Accordingly, we believe that it would be more appropriate to not replace the MCS indication as bridge to heart transplantation but to change it to a IIa class of recommendation with level of evidence B, as also concluded in the 2013 HF guidelines of the ACCF/AHA.<sup>12</sup>

Moreover, MCS systems should be considered as “destination therapy” for patients ineligible for transplantation, with a IIa class of recommendation, level of evidence B, because their benefit vs medical therapy has been shown in randomized trials. However, in Spain, this recommendation currently has limited applicability because the Spanish National Health System has widespread funding problems.

Finally, there was no recommendation regarding the implantation of temporary MSC devices in patients with cardiogenic shock. Regarding this aspect, the guidelines are particularly confusing because, although they recognize that MSC can be useful as a “bridge to decision”, the document states they it cannot be recommended as a treatment with proven efficacy for cardiogenic shock because no

randomized studies or metaanalyses have shown its benefit. This statement contrasts with the indication for temporary ventricular assistance in patients with cardiogenic shock in the above-mentioned 2013 guidelines of the ACCF/AHA, which awarded it a IIa class of recommendation, level of evidence B.

The main heart transplant-related innovation is the inclusion of the new indications and contraindications for heart transplant agreed by the International Society for Heart and Lung Transplantation (ISHLT),<sup>16</sup> which represent an adaptation of the guidelines to clinical practice. These changes concern the contraindications, 2 in particular. The first is the assertion that once severe pulmonary hypertension is classified as irreversible, we should consider the use of ventricular support. The second is the removal of the restriction on a history of treated neoplasm within 5 years prior to transplant, with the guidelines also recommending joint evaluation with oncology specialists. In addition, the guidelines explain that some contraindications are transient and treatable, noting that, with strict management, patients with HIV, hepatitis, Chagas disease, or tuberculosis can be considered suitable transplant candidates.

### MULTIDISCIPLINARY TEAM CARE

The guidelines stress that the key to the success of the HF management programs is ensuring continuity of care and thus list its characteristics and constituent elements. But perhaps the most novel aspect is the inclusion of the distinct roles that the professionals involved in HF management should play to help patients to acquire the necessary skills for self-management.

We consider it positive that the guidelines recommend that patients with HF perform aerobic exercise (class I, level of evidence A), independent of LVEF, because most Spanish cardiology services still lack cardiac rehabilitation programs and their implementation will be stimulated by these types of recommendations.

Another notable aspect is the benefit of correct discharge planning because programs incorporating early postdischarge follow-up drastically reduce the readmission rate.<sup>17</sup>

Finally, it is surprising that the recommendation that patients with stable HF and OMT be referred to primary care is classified as class IIb, level of evidence B, when the randomized studies behind this recommendation failed to find significant differences between primary care follow-up and specialized care,<sup>18,19</sup> suggesting that this approach should be classified as class IIa, level of evidence A.

### PALLIATIVE AND END-OF-LIFE CARE

This is 1 of the main challenges in the treatment of patients with HF and 1 of the sections with the least available evidence.

The aim of such care is to alleviate the symptoms and improve the quality of life of patients with refractory HF. The guidelines list a series of points that acts as a checklist to ensure that physicians remember oft-overlooked aspects. This approach not only covers medication, but also anticipated desires and emotional support to patients and their carers. Nonetheless, the available evidence is insufficient to establish concrete recommendations.

Lacking is the discussion of certain palliative therapies that can improve the quality of life of these patients, such as intermittent inotropic infusion and peritoneal dialysis.

Finally, the new guidelines introduce some risk scores that help health care staff to monitor symptoms and quality of life in palliative care, an interesting inclusion because these tools are also useful for the evaluation of therapy effectiveness.

### COMORBIDITIES

The section on comorbidities has improved both in length and depth, particularly in some of its subsections. This expansion

**Table 2**  
Key Points for the Treatment of Comorbidities

1.	For patients with angina and coronary heart disease, the treatment of choice is beta-blockers
2.	The presence of cachexia and sarcopenia contribute to morbidity and mortality
3.	Chemotherapy-related cardiotoxicity should be evaluated using imaging techniques, biomarkers, and multidisciplinary teams
4.	Central nervous system disorders (depression, stroke, and autonomic dysfunction) aggravate symptoms and can interfere with standard HF therapy
5.	Metformin is the drug of choice in patients with HF and DM; in conjunction with empagliflozin (SGLT2 inhibitor), it reduces HF hospitalizations and mortality of patients with DM and high cardiovascular risk
6.	HF-associated erectile dysfunction can be related to cardiovascular disease, psychological factors, or drug therapy. Phosphodiesterase 5 inhibitors can be useful but are contraindicated in patients under treatment with nitrates
7.	The presence of gout and arthritis is related to diuretic therapy and drugs worsening HF need to be avoided (nonsteroidal antiinflammatories)
8.	Intestinal potassium binders (patiromer and sodium zirconium cyclosilicate) can be useful for the treatment of hyperkalemia in HF
9.	The first 3 options for the treatment of hypertension are ACEIs (ARBs in the case of intolerance), beta-blockers, and MRAs
10.	Ferric carboxymaltose treatment of symptomatic patients with reduced LVEF and iron deficiency (serum ferritin < 100 µg/L or serum ferritin between 100 and 299 µg/L and transferrin saturation < 20%) is useful to alleviate symptoms and improve exercise capacity and quality of life
11.	Episodes of renal function deteriorations contribute to chronic renal injury and diuretic resistance
12.	Obesity favors HF development, above all in HFrEF, but is associated with lower mortality after HF diagnosis
13.	Sleep-disordered breathing conditions are common in HF but positive airway pressure therapies only benefit obstructive apnea
14.	The presence of valve diseases can cause or worsen HF. The choice between percutaneous and surgical approaches has to be made by a multidisciplinary "heart team" and be based on risk

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DM, diabetes mellitus; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter-2.

underlines their importance, as shown in the table reproduced and summarized here (Table 2). Notably, the guidelines have included for the first time intravenous treatment with ferric carboxymaltose for symptomatic patients with HFrEF and absolute or functional iron deficiency to improve symptoms, exercise capacity, and quality of life (class IIa, level of evidence A).

## CONCLUSIONS AND IMPLICATIONS

The new ESC guidelines for HF for 2016 are immensely useful. Despite the numerous gaps in evidence on certain aspects of HF diagnosis and treatment, the new findings and concrete practical recommendations are clearly presented, with most recommendations based on a high level of evidence. The presentation of a table at the end of the guidelines with the essential messages about what to do and what not to do is particularly valuable.

Although intense dissemination of the new recommendations is required, we predict that their application will have a positive impact on the quality and efficiency of care of patients with HF.

## APPENDIX. AUTHORS

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## CONFLICTS OF INTERESTS

None declared.

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