INTRODUCTION

In line with the policy on clinical practice guidelines established by the Executive Committee of the Spanish Society of Cardiology, the present article aims to discuss the most salient and novel features of the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure (HF). These guidelines update the recommendations of the prior version published 4 years ago in 2008 and include the new evidence that has emerged since then in the field of HF.

METHODS

The Clinical Practice Guidelines Committee of the Spanish Society of Cardiology established a working group composed of clinical cardiologists, electrophysiologists, cardiac surgeons and nursing staff, who were experts in the various aspects of HF covered by the ESC guidelines. The members of this working group were proposed by the Heart Failure and Transplant Section and the Working Group on Cardiac Resynchronization of the Spanish Society of Cardiology and by the Spanish Association of Cardiovascular Nursing, with the general aim of reviewing the evidence and recommendations provided in the ESC guidelines. All members of the working group were asked to analyze the guidelines, following a basic questionnaire that included the following points: a) analysis of the guidelines’ methodology; b) novel or salient contributions for clinical practice; c) analysis of the most positive and most questionable features of these contributions and their comparison with other guidelines on the topic; d) gaps in the document, and e) conclusions and implications for clinical practice in Spain. Based on these experts’ comments, a consensus document was drafted, which was approved by all the members of the working group. This document was sent for review to another group of experts, proposed by the Heart Failure and Transplant Section, whose comments were included in the final document.

GENERAL COMMENTS AND ANALYSIS OF THE METHODOLOGY

The main difference between the 2008 and 2012 guidelines is that, in the latter, all the recommendations, with their grades of recommendation and levels of evidence, are presented in tables whereas, in the former, there were few tables and the evidence was presented in the text. In the current guidelines, there are 121 recommendations, 80 general recommendations and 41 recommendations on the treatment of concomitant diseases in patients with HF. The proportion of recommendations with level
C evidence (expert consensus, without data from randomized, controlled studies or meta-analyses) is low in the current guidelines, representing only 43% of the total compared with 51% in the 2008 version. This indicates the strong level of evidence available in the management of HF, especially in the treatment of this disease, and enhances the value of the guidelines. The document obviously summarizes known and well-established evidence but, from the treatment point of view, tends to consider recommendations for drug classes and does not distinguish among specific drugs in each class, as discussed later in this article. There are some discrepancies when evaluating some recommendations, which are given a distinct grade with a similar level of evidence (for example, ivabradine in relation to other drugs). There are few novelties with respect to the previous guidelines on the topic of acute HF, which seems to receive less attention than chronic HF, probably due to the greater progress in knowledge of the latter.

**SALIENT OR NOVEL CONTRIBUTIONS**

The most important or novel contributions are listed in Table 1.

**CRITICAL EVALUATION OF SALIENT AND NOVEL CONTRIBUTIONS**

**Diagnosis of Heart Failure**

The criteria for the diagnosis of HF with preserved left ventricular ejection fraction (LVEF) or reduced LVEF are specified. While the presence of 3 criteria (symptoms typical of HF + signs typical of HF + reduced LVEF) are required for a diagnosis of HF with reduced LVEF, 4 criteria (symptoms typical of HF + signs typical of HF + normal or only mildly reduced LVEF and left ventricle not dilated + relevant structural heart disease and/or diastolic dysfunction) are required for a diagnosis of HF with preserved LVEF. Unlike previous versions of the guidelines, which assigned equal importance to symptom classification and functional capacity assessed with the New York Heart Association (NYHA) scale and that of the American Heart Association/American College of Cardiology (AHA/ACC) in relation to structural abnormalities (with stages A, B, C and D, based on the presence of risk factors, structural heart disease, symptoms of HF and refractory symptoms), the current version only adopts the classification based on symptomatic severity, which has the advantage of conceiving HF as a progressive and preventable disease. The table describing symptoms and signs and laboratory alterations is more exhaustive than descriptions in previous guidelines, providing an eminently practical view, which helps clinicians to take decisions on each particular factor. In the field of diagnosis, the classification of symptoms into more and less typical, and that of signs into more or less specific, has been adopted, aiding clarity and definition. Recommendations for all diagnostic tests (although with level C evidence) are also provided. For natriuretic peptides, the focus substantially differs from that in the 2008 guidelines, which assigned these peptides a major role in diagnosis. In the current guidelines, natriuretic peptide determination is mainly used as a “rule out” test when a diagnosis of HF is highly unlikely, and the guidelines provide distinct cut-points to exclude acute and chronic HF, with the aim of minimizing false-negative results. These guidelines introduce a novel approach, since they envisage 2 options in a diagnostic flowchart: the “echocardiographic” approach and the “natriuretic peptide” approach. In conclusion, the 2012 guidelines simplify concepts and avoid multiple classifications. The presentation of diagnostic tests with their grade of recommendation and level of evidence is a highly valuable resource.

One of the most salient gaps is the inclusion of comments on the particular features of right HF and of echocardiographic parameters to assess right ventricular function as well as S’, right TEI, right ventricular diameters, etc., as well as the stage-based AHA/ACC classification.

### Table 1

<table>
<thead>
<tr>
<th>Salient and Novel Aspects Found in the Guidelines</th>
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<tbody>
<tr>
<td>1. Better and more practical presentation of the diagnosis of HF, including algorithms and evaluation (advantages/disadvantages) of the distinct diagnostic tests</td>
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<tr>
<td>2. Pharmacological therapy: new recommendations on antialdosterone agents and ivabradine, and some changes in recommendations for classical drugs such as digitalis and vasodilators</td>
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<tr>
<td>3. Electrical therapy: extension of the indications for cardiac resynchronization therapy</td>
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<tr>
<td>4. Surgical treatment (coronary revascularization, circulatory support) and new percutaneous valvular procedures</td>
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<td>5. Importance of management and monitoring by multidisciplinary units</td>
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**Pharmacological Therapy**

The main novelty of the 2012 ESC guidelines concerning the pharmacological treatment of chronic HF is the introduction of ivabradine and modification of the grade of recommendation of 4 drug groups: mineralocorticoid receptor antagonists (MRA), angiotensin-receptor blocker (ARB), digoxin and the combination of isosorbide dinitrate and hydralazine. However, once again, the new guidelines unfortunately would have benefitted from more detailed discussion on the choice of certain drugs belonging to the same group or on how to use diuretics. Another important feature is that the recommendations on systolic HF are limited to patients with LVEF ≤40% or ≤35%, strictly following the inclusion criteria of the studies on which the guidelines are based, and consequently there are no recommendations for patients with mild systolic dysfunction (LVEF between 40% and 50%).

**Ivabradine**

The 2012 guidelines include the indication for ivabradine according to the original design of the ivabradine and outcomes in chronic heart failure (SHIFT) study, recommending its use in patients who, despite optimal treatment and maximum tolerated dose of beta-blockers (BB), angiotensin-converting enzyme (ACE) inhibitors and MRA have a heart rate in sinus rhythm of >70 bpm (recommendation IIa B). However, in February 2012, the European Medicines Agency granted a new indication for ivabradine in chronic HF patients with heart rate ≥75 bpm. It is difficult to understand how the guidelines assign class IIa to this recommendation when, in the main algorithm of the guidelines, the use of ivabradine is recommended if heart rate is >70 bpm. The guidelines should also have considered that, in patients with a heart rate of ≥75 bpm, a composite end-point of cardiovascular mortality and hospitalization for HF is reduced, and not only that of hospitalization. This issue has provoked a great deal of controversy, with opinions ranging from the belief that ivabradine has acquired too much importance in the clinical practice guidelines (with only 1 clinical trial in chronic HF) to the conviction that a IIb recommendation should be assigned to the use of this drug. In our opinion, the grade of recommendation is a sterile debate. The most important point of the SHIFT study is that it established heart rate as a highly potent prognostic marker and has therefore indicated a clear therapeutic goal. Consequently, once treatment with BB has been optimized, the use of ivabradine should be systematically considered if heart rate is >75 bpm.

**Mineralocorticoid Receptor Antagonists**

After the recent publication of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS), MRA were indicated (IA recommendation) in patients with symptomatic...
HF and LVEF ≤35%, displacing ARB. What the guidelines do not specify is the first-line choice of drug, whether spironolactone and eplerenone, giving the impression that all MRAs are equal. It would have been more reasonable to recommend each drug in the particular clinical scenario in which its efficacy had been demonstrated, as well as recommending recent US guidelines. Therefore, in our opinion and, at the present moment, the choice of spironolactone or eplerenone will depend on the following: a) the patient’s clinical profile (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS], EMPHASIS or Randomized Aldactone Evaluation Study [RALES]); b) the safety profile, and c) cost (higher for eplerenone, although this will be changed by the imminent introduction of the generic drug). The indication of an MRA in asymptomatic patients with severe ventricular dysfunction and in those with mild-moderate left ventricular dysfunction remains to be clarified.

Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers

The grade of recommendation and level of evidence are maintained for both drug classes: in patients with LVEF ≤40%, independently of the presence or absence of symptoms and their severity, both drug groups are assigned a class I recommendation with level A evidence. Beta-blockers with clinical evidence in chronic HF include carvedilol, bisoprolol and metoprolol. Evidence for the use of nebivolol is less robust. A possible shortcoming in the table of recommendations is that it fails to specify that it is these BB, and not others, that are indicated. Equally, as in the case of MRA, the table fails to specify their use in patients with a LVEF between 40% and 50%, due to lack of evidence.

Angiotensin Receptor Blocker

Several trials have shown that ARB have the same beneficial effect as ACE inhibitors in patients with HF with reduced LVEF. Nevertheless, if the beneficial effect obtained with double blockade of the renin-angiotensin-aldosterone system by combining an ACE inhibitor with an ARB vs. the combination of an ACE inhibitor and an MRA, the benefits obtained with this latter combination are more evident and robust. Consequently, the first-choice combination is an ACE inhibitor plus an MRA (vs an ACE inhibitor + ARB). The guidelines establish a class IA recommendation for ARB in patients with intolerance to ACE inhibitors or MRA. However, given the results of studies in chronic HF and of others in postinfarction dysfunction, which indicate similar efficacy to ACE inhibitors, perhaps an ARB could have been recommended as initial treatment with the same level of evidence as ACE inhibitors, rather than only when the latter cannot be used.

Electrical Therapy: Implantable Cardioverter-Defibrillators and Resynchronization Therapy

Implantable Cardioverter-Defibrillators

The 2012 guidelines contain few changes with respect to the 2008 version. The clearest indication for an implantable cardioverter-defibrillator (ICD) is probably secondary prevention for survivors of ventricular fibrillation or ventricular tachycardia with hemodynamic instability who are expected to survive >1 year. The slight change introduced in the 2012 version is the expression “irrespective” of LVEF, while in 2008, the indication was restricted to patients with LVEF ≤40%. Implantation of an ICD for primary prevention is recommended in symptomatic patients with LVEF ≤35% despite 3 months of optimal medical therapy (this observation was not made in the previous version and is pertinent, since this treatment improves LVEF in 20–25% of patients with severe ventricular dysfunction); the recommendation is IA in ischemic patients (due to the strong evidence in several trials) and IB in non-ischemic patients (which is clearly debatable, since none of the 3 randomized trials showed a significant benefit).²⁰⁻¹²

Cardiac Resynchronization Therapy

The novelty of these guidelines is the incorporation of the clinical experience provided by studies of resynchronization in early phases of HF,²¹⁻²⁵ in patients in NYHA functional class I-II. In general, the recommendations for cardiac resynchronization therapy (CRT) are based on functional classes (ambulatory III and IV) and the presence or absence of left bundle branch block (LBBB) in patients with broad QRS. These criteria should be accompanied by LVEF ≤35% in functional class III-IV and LVEF ≤30% in class II. In the presence of LBBB, recommendations are class I, and with other QRS morphologies, recommendations are class IIa. All these variants may hamper the practical application of these guidelines. Moreover, detailed reading of these recommendations leads to serious doubts on their scientific justification. Concerning functional class, extreme functional classes are not sufficiently represented in clinical trials and consequently the patients who can unequivocally benefit from CRT are those in functional classes II (with LVEF ≤30%) and III (with LVEF ≤35%). The factor most strongly affecting the benefit of CRT is QRS duration. In all trials, patients with a broader QRS, with a cut-off of around 150 ms, are the only patients who derive a benefit from CRT; indeed, no group with QRS <150 ms shows even a tendency to derive a benefit. This finding was confirmed by 2 meta-analyses disseminated in 2011.²⁶⁻²⁷ Following this evidence, numerous authors believed that the class I recommendation for CRT should only include patients with QRS >150 ms.²⁶⁻²⁷ In contrast, the group with QRS <150 ms, who are well represented in trials, could only receive a class Ib recommendation, according to which CRT “could be considered” in the absence of sufficient evidence.

QRS morphology, the criterion chosen by these guidelines to assign a class I recommendation, seems to be associated with the success of CRT, but has less statistical consistency than QRS duration. The presence of LBBB is desirable in candidates for CRT, but seems to be a less determining factor. For morphologies without LBBB, a QRS duration >150 ms is required (IIa A recommendation). In the subgroup analysis, patients with a non-sinus rhythm (whether due to atrial fibrillation or pacemaker-dependency) do not seem to benefit from CRT.²⁸ Therefore, it seems logical that in these categories CRT be assigned a lower level of recommendation in the 2012 ESC guidelines than in the version updated in 2010, even though these patients account for more than 20% of currently performed implantations.

Simplifying, we believe that the indication of CRT only deserves a class I level A recommendation in patients in sinus rhythm and marked LVEF depression, with functional class II-III, under optimal therapy, and QRS width >150 ms (preferably with LBBB morphology). The indication in patients with QRS between 120 ms and 150 ms should only be taken as marginally beneficial.

Surgery, Ventricular Assist Devices, Transplantation and Percutaneous Procedures

The 2012 ESC guidelines contain novelties in the field of coronary and valvular surgery, and percutaneous implantation of valvular and circulatory assist devices, but very few on heart transplantation.

Coronary Revascularization

Surgical revascularization in patients with systolic dysfunction, angina and 2- or 3-vessel disease (including the anterior descending artery) who are suitable for surgery is recommended (IB). The surgical arm of the Surgical Treatment for Ischemic Heart Failure (STICH) trial is mentioned; the benefit of surgery in reducing mortality and
hospitalization is highlighted and the extension of this indication to other patient groups is proposed. Nevertheless, in this trial, the primary outcome only reached statistical significance after an adjustment was made once the trial was underway. Reference to the “ Appropriateness Criteria for Coronary Revascularization”20, jointly established by several American societies of cardiology and surgery in 2009, is lacking. The role of surgery in the absence of angina or viable myocardium, as well as the value of tests to detect viability, are unclear.

Valvular Surgery

The specific indications for valvular surgery are contained in recent guidelines.21 For the first time in these guidelines, the option of percutaneous implantation of an aortic prosthetic valve is considered in patients at high surgical risk and the door is opened to percutaneous valvular repair in patients with an indication for this procedure considered inoperable or at high surgical risk.

Ventricular Reconstruction

The guidelines support the conclusion of the STICH study, which showed no benefit when surgical reconstruction was associated with coronary revascularization; however, there is no mention of the controversy generated after the STICH study, which placed its conclusions in doubt22 nor is there any mention of the uncertainties aroused by the abundant literature contradicting the results of that study when applied to a real-life population.22 The guidelines explicitly advise against the use of external constraint devices, while providing no evidence to support this recommendation and ignoring randomized clinical trials that have shown their efficacy in the medium-term in specific groups of patients.21

Heart Transplantation

The 2012 guidelines do not discuss important features of transplantation in greater detail or provide new information, presenting an unoriginal—even somewhat out-of-date—table of indications and contraindications. A more specific and detailed table, with conventional criteria, clinical criteria and unusual transplantation criteria, which would aid non-specialized cardiologists, is lacking.24

Mechanical Circulatory Support

A left ventricular assist device (LVAD) or bi-ventricular assist device (BiVAD) are assigned a class IB recommendation in patients with end-stage HF as a bridge to transplantation, and a IIa B recommendation in carefully selected patients not eligible for transplantation (destination therapy). The use of LVAD in 2 distinct clinical scenarios is recommended: a) in acute HF or cardiogenic shock, in addition to intra-aortic balloon counterpulsation, the option of LVAD with extracorporeal membrane oxygenation is recommended for the first time as a bridge to recovery or a bridge to decision, and b) in end-stage HF, criteria for indicating a long-term LVAD, inspired in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (ReMATCH) study,25 are included for the first time.26 A debatable point is that the guidelines do not distinguish between short- and long-term LVAD. There is no mention that the reason for including LVAD as the recommended treatment in patients with end-stage HF are the good results obtained with continuous-flow LVAD in contrast to pulsatile devices.26 An LVAD or BiVAD is recommended (class IB) as a bridge to transplantation, but there is no reference to any studies that have evaluated the use of a BiVAD as a bridge to transplantation. Equally, there is no mention of which type of mechanical support device should be used, when there are differences among the available devices, which could lead to lack of comparability in the results.26

Myocardial Regeneration With Stem Cells

Despite the existence of several studies and meta-analyses with positive results27—especially in patients with postinfarction systolic dysfunction, which for other treatments would lead to a class I recommendation with level A or B evidence—, the guidelines make no mention of this type of therapy.

Comorbidities and Multidisciplinary Follow-up

This section is one of the parts of the guidelines with the least strength of evidence.

Comorbidities

A novelty of the current version is the inclusion of iron deficiency as an emerging comorbidity. Also notable is the importance given to other frequent chronic conditions in HF patients, such as erectile dysfunction, depression, sleep-related disorders (central and obstructive sleep apnea syndrome) and—especially valuable novel contribution—the proposed algorithms for the management of angina and hypertension in more clearly defined tables. Specific recommendations for the management of diabetes mellitus have disappeared. A substantial change in the 2012 version is the recommendation (class III level A evidence) for the use of glitazones in HF. After the benefit observed in the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial,28 it would have been especially useful to have a grade of recommendation on when and in whom the presence of iron deficiency should be evaluated, the recommended criteria for a diagnosis of iron deficiency, and the grade of recommendation for initiating intravenous therapy.

Holistic Management

The importance of HF units and programs are not described in detail, despite receiving a IA recommendation, nor are the distinct organizational models mentioned. In our opinion, the important role of specialist HF nurses, who frequently lead these teams, is not highlighted. It would be appropriate to stress the need for specialized nurses, as well as their fundamental role in the optimization and application of treatment and health education for patients and their carers. Equally, there are no recommendations on the approach to specific situations such as management during pregnancy or the use of contraception in patients with HF. Following the reasoning of other recommendations (especially those concerning pharmacological treatment) a class IA recommendation for physical exercise could be questioned, since, without ignoring the fact that most evidence points to a clear benefit, the evidence supporting the recommendation includes only 1 multicenter trial in which the primary composite endpoint was only significant after adjustment by prognostic variables.

GAPS IN THE GUIDELINES

Gaps in the guidelines are listed in Table 2.

CONCLUSIONS AND IMPLICATIONS

Despite the gaps and controversial recommendations discussed in each of the points mentioned in these comments, in our opinion, the new 2012 ESC guidelines on heart failure constitute a highly valuable document that clearly presents the latest evidence and provides practical and specific recommendations based mainly on a high level of evidence. Although we would always like to find an answer to any question, we should remember that a clinical practice guideline is not an “absolute truth” but is rather, as its name implies, a “guide” or aid
Gaps in the Guidelines

1. Inclusion of comments on the particular features of right heart failure and echocardiographic parameters for evaluating right ventricular function (only TAPSE is included)
2. Importance of and reference to classification in stages (A, B, C and D) of the AHACF
3. Scarce attention to acute heart failure
4. Greater attention to the choice of some drugs belonging to the same group (epilone with or vs spironolactone, angiotensin-converting enzyme inhibitors vs angiotensin II receptor antagonists or the distinct beta-blockers)
5. Management of patients with mild-moderate systolic heart failure (LVEF 40%-50%). There is no discussion on how to treat these patients, although common sense indicates that they would possibly benefit from the same drugs as those in the aim of halting or delaying progression of systolic dysfunction. Equally, there are no data on how to proceed when LEVF improves or returns to normal, exceeding 50%
6. Influence of cost-effectiveness considerations on the indications for implantable Cardioverter-defibrillators and resynchronization therapy, as well as more specific practical recommendations on indications based on the selection of subgroups with a greater or lesser grade of evidence.
7. Role of myocardial revascularization surgery in the absence of angina or viable myocardium, as well as the value of tests to detect myocardial viability
8. Indications on the specific type of ventricular assist device that should be used in each scenario
9. References to the utility of stem cells, which are not even mentioned
10. Greater attention to the characteristics of multidisciplinary monitoring programs and, especially, the role of nursing as a fundamental component of these programs

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