

Editorial

Comments on the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012. A Report of the Task Force of the Clinical Practice Guidelines Committee of the Spanish Society of Cardiology

Comentarios a la guía de práctica clínica de la ESC sobre diagnóstico y tratamiento de la insuficiencia cardíaca aguda y crónica 2012. Un informe del Grupo de Trabajo del Comité de Guías de Práctica Clínica de la Sociedad Española de Cardiología

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INTRODUCTION

In line with the policy on clinical practice guidelines established by the Executive Committee of the Spanish Society of Cardiology,¹ 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).² These guidelines update the recommendations of the prior version published 4 years ago in 2008³ 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.² 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

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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.³ 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,³ 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,³ 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 guidelines² 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 S₁, right TEI, right ventricular diameters, etc., as well as the stage-based AHA/ACC classification.

Table 1

Salient and Novel Aspects Found in the Guidelines

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

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 $\leq 40\%$ or $\leq 35\%$, 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,⁴ 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 IB 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.⁵⁻⁷ 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),⁸ MRA were indicated (IA recommendation) in patients with symptomatic

HF and LVEF $\leq 35\%$, 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.⁹ 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 $\leq 40\%$, 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 strong. 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.² 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.⁸ 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 $\leq 40\%$. Implantation of an ICD for primary prevention is recommended in symptomatic patients with LVEF $\leq 35\%$ 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).^{10–12}

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,^{13–15} 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 vs. II) and the presence or absence of left bundle branch block (LBBB) in patients with broad QRS. These criteria should be accompanied by LVEF $\leq 35\%$ in functional class III-IV and LVEF $\leq 30\%$ 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.¹⁶ 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 $\leq 30\%$) and III (with LVEF $\leq 35\%$). 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.^{17,18} Following this evidence, numerous authors believed that the class I recommendation for CRT should only include patients with QRS >150 ms.^{16–18} In contrast, the group with QRS <150 ms, who are well represented in trials, could only receive a class IIb 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.¹⁵ 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) trial¹⁹ 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.²³

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. ²⁵ 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—an 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

Table 2
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 AHA/ACC
3.	Scarce attention to acute heart failure
4.	Greater attention to the choice of some drugs belonging to the same group (eplerenone 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, with the aim of halting or delaying progression of systolic dysfunction. Equally, there are no data on how to proceed when LVEF 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 in the guidelines, despite the existence of studies and meta-analyses with positive results, especially in patients with postinfarction systolic dysfunction
10.	Greater attention to the characteristics of multidisciplinary monitoring programs and, especially, the role of nursing as a fundamental component of these programs

AHA, American Heart Association; ACC, American College of Cardiology; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion

for clinical decision making, which should be based on evidence and clinical judgment. The application of the new recommendations, for which intense dissemination is required, should have a positive impact on the quality and efficiency of the care of patients with HF.

CONFLICT OF INTERESTS

M. Anguita: Presentations (Pfizer, Rovi, Servier). E. Pérez de la Sota: Training (Cardiolink). F. Ridocci: Presentations (Pfizer, Menarini, Servier, Novartis, Asta-Zeneca, Boehringer). J. Lupón: Presentations (Servier). D. Pascual: Presentations (Pfizer, Almirall, Servier). J.R. González-Juanatey: Presentations (MSD, Rovi, Servier, Pfizer). F. Worner: Expert (Rovi, Servier). A. López Granados: Presentations (Pfizer, Rovi, Servier).

REFERENCES

- Anguita M, Fernández-Ortiz A, Worner F, Alonso A, Cequier A, Comín J, et al. La Sociedad Española de Cardiología y las guías de práctica clínica de la SEC: hacia una nueva orientación. *Rev Esp Cardiol.* 2011;64:795-6.
- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012 Jun 26 [Epub ahead of print].
- Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29:2388-442.
- Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875-85.
- Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet.* 2010;376:886-94.

- Swedberg K, Komajda M, Bohm M, Borer J, Robertson M, Tavazzi L, et al. Effects on Outcomes of Heart Rate Reduction by Ivabradine in Patients With Congestive Heart Failure: Is There an Influence of Beta-Blocker Dose?: Findings From the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) Study. *J Am Coll Cardiol.* 2012; Feb 22 [Epub ahead of print].
- Bohm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol.* 2012 May 11 [Epub ahead of print].
- Zannad F, McMurray JJ, Krum H, Van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364:11-21.
- Butler J, Ezekowitz JA, Collins SP, Givertz MM, Teerlink JR, Walsh MN, et al. Update on aldosterone antagonists use in heart failure with reduced left ventricular ejection fraction. *Heart Failure Society of America Guidelines Committee. J Card Fail.* 2012;18:265-81.
- Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med.* 2004;350:2151-8.
- Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* 2005;352:225-37.
- Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta analysis. *Europace.* 2010;12:1564-70.
- Linde C, Abraham WT, Gold MR, St John SM, Ghio S, Daubert C, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol.* 2008;52:1834-43.
- Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart failure events. *N Engl J Med.* 2009;361:1329-38.
- Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med.* 2010;363:2385-95.
- Stevenson WG, Hernandez AF, Carson PE, Fang JC, Katz SD, Spertus JA, et al; Heart Failure Society of America Guideline Committee. Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America Guideline Committee. *J Card Fail.* 2012;18:94-106.
- Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Arch Intern Med.* 2011;171:1454-62.
- Stavarakis S, Lazzara R, Thadani U. The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. *J Cardiovasc Electrophysiol.* 2012;23:163-8.
- Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med.* 2011;364:1607-16.
- Patel MR, Dehmer GJ, Hirshfeld J, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2009;53:530-3.
- Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the Management of Valvular Heart Disease (Version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2012. doi:10.1093/eurheartj/ehs109.
- Buckberg G, Athanasuleas CL, Wechsler AS, Beyersdorf F, Conte JV, Strobeck JE. The STICH trial unravelled. *Eur J Heart Fail.* 2010;12:1024-7.
- Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *J Thorac Cardiovasc Surg.* 2011;141:905-16.
- Banner NR, Bonser RS, Clark AL, Clark S, Cowburn PJ, Gardner R, et al. UK guidelines for referral and assessment of adults for heart transplantation. *Heart.* 2011;97:1520-7.
- Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. The fourth INTERMACS annual report: 4,000 implants and counting. *J Heart Lung Transplant.* 2012;31:117-26.
- Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, et al. Results of the post-US. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: A prospective study using the INTERMACS (interagency registry for mechanically assisted circulatory support). *J Am Coll Cardiol.* 2011;57:1890-8.
- Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. *Circulation.* 2012 Jun 22 [Epub ahead of print].
- Anker SD, Comin-Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med.* 2009;361:2436-48.