

2010 Focused Update of ESC Guidelines on device therapy in heart failure

An update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy

Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association

Authors/Task Force Members, Kenneth Dickstein (Chairperson) (Norway)*, Panos E. Vardas (Chairperson) (Greece)*, Angelo Auricchio (Switzerland), Jean-Claude Daubert (France), Cecilia Linde (Sweden), John McMurray (UK), Piotr Ponikowski (Poland), Silvia Giuliana Priori (Italy), Richard Sutton (UK), Dirk J. van Veldhuisen (Netherlands)

ESC Committee for Practice Guidelines (CPG), Alec Vahanian (Chairperson) (France), Angelo Auricchio (Switzerland), Jeroen Bax (The Netherlands), Claudio Ceconi (Italy), Veronica Dean (France), Gerasimos Filippatos (Greece), Christian Funck-Brentano (France), Richard Hobbs (UK), Peter Kearney (Ireland), Theresa McDonagh (UK), Bogdan A. Popescu (Romania), Zeljko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendera (Poland), Panos Vardas (Greece), Petr Widimsky (Czech Republic)

Document Reviewers, Michal Tendera (CPG Review Coordinator) (Poland), Stefan D. Anker (Germany), Jean-Jacques Blanc (France), Maurizio Gasparini (Italy), Arno W. Hoes (Netherlands), Carsten W. Israel (Germany), Zbigniew Kalarus (Poland), Bela Merkely (Hungary), Karl Swedberg (Sweden), A. John Camm (UK)

The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines

Keywords: Guidelines • Heart failure • Devices • Cardiac resynchronization therapy • Biventricular pacing • Implantable cardioverter defibrillator • Left ventricular assist device • CRT • CRT-P • CRT-D • ICD • LVAD

* Corresponding authors:

Kenneth Dickstein, 1. Stavanger University Hospital, Stavanger, Norway; 2. Institute of Internal Medicine, University of Bergen, Bergen, Norway. Tel: +47 51519453, Fax: +47 51 519921, Email: kenneth.dickstein@med.uib.no

Panos E. Vardas, Department of Cardiology, Heraklion University Hospital, PO Box 1352 Stavrakia, GR-711 10 Heraklion (Crete), Greece. Tel: +30 2810 392706, Fax: +30 2810 542 055, Email: cardio@med.uoc.gr

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the *European Heart Journal* and the party authorized to handle such permissions on behalf of the ESC.

Disclaimer. The ESC Guidelines represent the views of the ESC and were arrived at after careful consideration of the available evidence at the time they were written. Health professionals are encouraged to take them fully into account when exercising their clinical judgement. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

© The European Society of Cardiology 2010. All rights reserved. For permissions please email: journals.permissions@oxfordjournals.org.

Table of Contents

1. Introduction	2678
2. Cardiac resynchronization therapy with pacemaker/ defibrillator function in patients with heart failure in NYHA function class III/IV	2678
3. Cardiac resynchronization therapy with defibrillator function in patients with heart failure in NYHA function class I/II	2680
4. Cardiac resynchronization therapy with pacemaker/ defibrillator function in patients with heart failure and permanent atrial fibrillation	2681
5. Cardiac resynchronization therapy with pacemaker/ defibrillator function in patients with heart failure and a conventional pacemaker indication	2683
6. Left ventricular assist device as destination therapy for patients with severe heart failure ineligible for cardiac transplantation	2684
7. Evidence tables	2684
References	2686

Abbreviations

AF	atrial fibrillation
AV	atrio-ventricular
CPG	Committee for Practice Guidelines
CRT	cardiac resynchronization therapy
CRT-P	CRT with pacemaker function
CRT-D	CRT with defibrillator function
CTX	cardiac transplantation
CV	cardiovascular
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
HF	heart failure
HFA	Heart Failure Association
Hosp	hospitalization
ICD	implantable cardioverter defibrillator
LBBB	left bundle branch block
LV	left ventricular
LVAD	left ventricular assist device
LVEDD	left ventricular end-diastolic diameter
LVEF	left ventricular ejection fraction
LVESi	left ventricular stroke volume index
LVESV	left ventricular end-systolic volume
6MWT	6 min walk test
NA	not applicable
NIH	National Institutes of Health
NS	not significant
NYHA	New York Heart Association
OMT	optimal medical therapy
pVO ₂	peak oxygen consumption
QoL	quality of life
RBBB	right bundle branch block
RCT	randomized clinical trial
SR	sinus rhythm
VE/CO ₂	ventilation/carbon dioxide ratio

1. Introduction

The Committee for Practice Guidelines (CPG) of the European Society of Cardiology recognizes that new evidence from clinical research trials may impact on current recommendations. The current heart failure (HF) guidelines¹ were published in 2008 and the cardiac pacing guidelines in 2007.² In order to keep these guidelines up to date, it would be appropriate to modify the recommendations and levels of evidence according to the most recent clinical trial evidence. This Focused Update on the use of devices in heart failure 2010 is the first publication of its kind from the CPG.

Practice Guideline recommendations should represent evidence-based medicine. Traditionally, these recommendations are based on the outcomes in the cohort of patients described by the inclusion criteria in the protocols of randomized clinical trials (RCTs). More recently, based on the fact that the characteristics of the patients actually included in a trial may differ substantially from the eligibility criteria, Guideline Task Force members frequently favour restricting the applicability of these recommendations to the clinical profile and outcomes of the enrolled cohort, representing a more accurate interpretation of the evidence provided by a trial's result.

In contrast to previous guidelines, this focused update considers the characteristics of the patients included in the trials and contains several examples. In MADIT-CRT, although the protocol permitted inclusion of patients in both New York Heart Association (NYHA) I and II function class, only 15% of the patients included in this trial were classified as NYHA I, many of whom had been previously symptomatic. Similarly, although the inclusion criteria permitted randomization of patients with a QRS width of ≥ 130 ms, the favourable effect on the primary endpoint was limited to patients with a QRS width of ≥ 150 ms, a prospective, pre-specified cut-off. The text accompanying these recommendations explains and justifies the decisions to diverge from a traditional recommendation based strictly on the protocol inclusion criteria. The Task Force hopes that the users of the Guidelines will appreciate that this adjustment provides a more realistic application of the trial evidence to daily clinical practice.

2. Cardiac resynchronization therapy with pacemaker/defibrillator function in patients with heart failure in New York Heart Association function class III/IV

Evidence-based efficacy of cardiac resynchronization therapy in New York Heart Association class III/IV patients

The management of patients with HF represents a substantial economic burden and hospitalization is responsible for $>50\%$ of this expense.³ The initial expense of device implantation must be weighed against measures of short- and long-term efficacy with

regard to survival, morbidity, and quality of life.⁴ The effective use of limited health care resources necessitates identification of the characteristics of the patient population most likely to benefit from cardiac resynchronization therapy (CRT) and treatment strategy should target these patients for device implantation.

The clinical effects of long-term CRT have been evaluated in a large number of randomized multi-centre trials with crossover or parallel treatment assignment,^{5–11} using CRT pacemakers (CRT-P) or CRT-implantable cardioverter defibrillator (ICD) devices (CRT-D). Practice with regard to the choice of the CRT device varies widely between countries.⁴ Meta-analyses were also published,^{12–15} suggesting that the most efficacious option in patients with HF and low left ventricular ejection fraction (LVEF) would be a CRT-D. The usual study enrolment criteria were: NYHA function class III or IV despite optimal pharmacological treatment, LVEF $\leq 35\%$, sinus rhythm (SR), left ventricular (LV) dilatation but with varying definitions, and QRS duration $\geq 120/\geq 130$ ms.

Impact of cardiac resynchronization therapy on symptoms and exercise tolerance

All RCTs have confirmed a significant alleviation of symptoms and increase in exercise capacity conferred by CRT. On average, NYHA function class decreased by 0.5–0.8 points, the 6 min walk distance increased by 20%, and peak oxygen consumption increased by 10–15%. The functional benefits and quality of life improvements were sustained.^{11,16,17}

Impact of cardiac resynchronization therapy on morbidity

In the COMPANION trial, CRT with or without an ICD, lowered the combined endpoint of all-cause mortality and rehospitalization for HF by 35–40%, mainly driven by the 76% lower rate of hospitalizations.¹⁰ In CARE-HF, CRT-P lowered the proportion of unplanned hospitalizations for worsening HF by 52%, and the number of unplanned hospitalizations for major cardiovascular events by 39%.¹¹

Impact of cardiac resynchronization therapy on mortality

CARE-HF and COMPANION were trials powered to examine the effects of CRT on combined primary endpoints of morbidity and mortality.^{10,11} In COMPANION, CRT-D was associated with a significant decrease in all-cause mortality (relative risk reduction: 36%; $P = 0.003$), while the 24% relative risk reduction in mortality associated with CRT-P was nearly statistically significant ($P = 0.059$). A limitation of COMPANION was the absence of pre-specified analysis to compare CRT-D and CRT-P, precluding demonstration of the superiority of one CRT strategy over the other. In CARE-HF, where only CRT-P was assessed, a 36% relative reduction in the risk of death ($P < 0.002$) was observed after a mean follow-up time of 29 months. In the CARE-HF extension study, a relative risk reduction of 40% ($P < 0.0001$) was observed, mainly due to a marked reduction in HF-related deaths.¹⁷

Impact of cardiac resynchronization therapy on cardiac function and structure

A consistent finding in the randomized trials designed with up to 6 months of follow-up has been an up to 15% absolute reduction in LV end-diastolic diameter and an up to 6% increase in LVEF following CRT.^{16,18} In the CARE-HF study, the mean reduction in LV end-systolic volume was 18% at 3 months and 26% after 18 months of CRT. Similarly, the mean LVEF increase was 3.7% at 3 months increasing to 6.9% at 18 months.¹¹ The effect was significantly greater in patients with non-ischaemic than in those with ischaemic heart disease. These observations provide consistent evidence of a substantial, progressive, and sustained reverse remodelling effect conferred by CRT.

Ambulatory patients in New York Heart Association function class IV

COMPANION enrolled 217 NYHA class IV patients.¹⁹ Patients were required to have had no scheduled or unscheduled admissions for HF during the last month and are termed 'ambulatory' class IV patients with a life expectancy of >6 months. *Post hoc* analysis found that time to all-cause mortality or first all-cause hospitalization was significantly improved by both CRT-P and CRT-D as compared with optimal medical treatment. No significant benefit was observed on all-cause mortality. The 2-year mortality rates were 55% and 45% with CRT-D and CRT-P, respectively, compared with 62% in the control group. A significant functional improvement was also documented. These data support the use of CRT to improve morbidity (but not mortality) in ambulatory class IV patients.

QRS morphology: left bundle branch block vs right bundle branch block

Favourable outcome was defined as freedom from death or major cardiovascular event in CARE-HF.¹⁸ A baseline typical left bundle branch block (LBBB) pattern predicted a favourable outcome. By multivariable analysis, prolonged PR interval and right bundle branch block (RBBB) were the only predictors of non-favourable outcome. The 5% of patients with RBBB had a particularly high event rate.

Cardiac resynchronization therapy with defibrillator function in patients with a conventional indication for an implantable cardioverter defibrillator

One large study, MIRACLE ICD⁹ and one large meta-analysis¹⁵ support the choice of a CRT-D in patients in NYHA class III/IV, with LVEF of $\leq 35\%$, QRS width of ≥ 120 ms with a conventional indication for an ICD.

Key points

- New: LV dilatation no longer required in the recommendation.
- New: class IV patients should be ambulatory.
- New: reasonable expectation of survival with good functional status for >1 year for CRT-D.
- Evidence is strongest for patients with typical LBBB.
- Similar level of evidence for CRT-P and CRT-D.

Recommendation in patients with heart failure in New York Heart Association function class III/IV

Recommendation	Patient population	Class ^a	Level ^b	Ref. ^c
CRT-P/CRT-D is recommended to reduce morbidity and mortality ^d	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms, SR Optimal medical therapy Class IV patients should be ambulatory ^e	I	A	5–19

^aClass of recommendation.

^bLevel of evidence.

^cReferences.

^dReasonable expectation of survival with good functional status for >1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.

^eNo admissions for HF during the last month and a reasonable expectation of survival >6 months.

CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

3. Cardiac resynchronization therapy with defibrillator function in patients with heart failure in New York Heart Association function class I/II

Clinical evidence in mildly symptomatic or asymptomatic patients

The role played by CRT in patients presenting with no or only mild manifestations of HF, a depressed LVEF and a wide QRS complex, has been addressed in three trials. The MIRACLE ICD II⁹ trial enrolled 186 candidates for ICD, who presented in NYHA function class II and in SR, and whose LVEF was ≤35%, QRS duration ≥130 ms, and LV end-diastolic diameter ≥55 mm. All patients received a CRT-D, and CRT was randomly activated in 85 patients. Despite the development of significant reverse LV remodelling, their exercise capacity was not increased. The large MADIT-CRT²⁰ and REVERSE²¹ randomized trials evaluated the incremental benefit conferred by CRT in medically optimally treated patients. MADIT CRT enrolled 1820 patients in NYHA function class I (15%) of ischaemic aetiology or II (84%) of any aetiology and SR, whose LVEF was ≤30% and QRS duration ≥130 ms.²⁰ Using a 2:3 randomization scheme, 731 patients were assigned to receive an ICD and 1089 received a CRT-D. The primary endpoint was a composite of death from any cause and non-fatal HF-related adverse events. During a mean follow-up of 2.4 years, the relative risk of sustaining a primary endpoint was reduced by 34% in the CRT-D-treated group, a benefit attributable primarily to a 41% decrease in HF-related adverse events. The ~3% annual mortality was similar in both study groups. MADIT-CRT was stopped prematurely by the Data Safety Monitoring Board when a rigorous, pre-specified, stopping boundary was crossed, ultimately, at the $P < 0.001$ level.

REVERSE enrolled 610 patients treated with an optimal medical regimen, in NYHA function class I or II and SR, whose LVEF was ≤40%, QRS duration ≥120 ms, and LV end-diastolic diameter ≥55 mm.²¹ All patients had a history of HF symptoms. They underwent implantation of a CRT-D or CRT-P, according to the investigator's recommendations, though, ultimately, only 15% of patients received a CRT-P. Patients were randomly assigned to CRT activated versus CRT off. The primary endpoint was the percentage of clinically worsened patients, ascertained by the use of a composite endpoint, and the powered secondary endpoint was echocardiographic change in LV end-systolic volume index. After 12 months, no significant difference was observed in the primary endpoint. However, a significant degree of reverse LV remodelling was observed among the patients assigned to CRT, manifested by decreases in the LV end-systolic and -diastolic volumes and an increase in LVEF.

The European sample of REVERSE comprised 262 patients, whose follow-up was extended to 24 months.²² In that population, significantly fewer patients assigned to CRT worsened clinically. Similarly, the time to first hospitalization for management of HF or to death from any cause was significantly delayed. The mean LV end-systolic volume index was significantly smaller in the group assigned to CRT.

In MADIT-CRT, the data reveal substantial differences in outcome according to the presence or absence of LBBB. It is also noteworthy that, in *pre-specified subgroup analyses* of data collected in MADIT CRT²⁰ and REVERSE,²³ the patients whose QRS duration was ≥150 ms derived the greatest benefit from CRT. In MADIT-CRT, women with LBBB demonstrated a particularly favourable response. Considering limited resources, it would be prudent to target the population most likely to respond favourably. In patients with mild symptoms and a QRS width of 120–150 ms, clinicians may wish to assess other criteria associated with a favourable outcome such as dyssynchrony by echocardiography, LV dilatation, LBBB, non-ischaemic cardiomyopathy, or recent NYHA class III symptoms.

LV remodelling and clinical outcomes

Paired echocardiographic studies were obtained in nearly all patients in MADIT CRT ($n = 1809/1820$) and analysed at a core laboratory. Eighty-four per cent of patients were in NYHA function class II.²⁴ Patients were on optimal medical therapy. Consistent with the echocardiographic studies from CARE-HF and REVERSE, substantial improvements in LV size and function, LVEF, RV function, left atrial size and mitral regurgitation severity were observed in patients treated with CRT compared with ICD only. Although these findings were consistent across all subgroups, the improvements in volumes were greatest in patients with a QRS width of ≥ 150 ms, patients with LBBB, patients with non-ischaemic aetiology, and in female patients. These findings were strongly concordant with and predictive of the primary outcome of death or a HF event and suggest a compelling cardiac structural and functional mechanism by which CRT therapy improves outcomes.

These results suggest that in the long-term, CRT lowers the risk of HF-related adverse clinical events and prevents or reduces the progression of disease by reverse LV remodelling. However, further studies are needed to determine whether reverse LV remodelling leads to better long-term clinical outcomes and whether survival is increased by CRT-D in patients with mild symptoms.

New York Heart Association class I

MADIT-CRT²⁰ and REVERSE^{21,22} enrolled a small proportion of asymptomatic patients, only 15% and 18%, respectively. It is not clear exactly how many patients had a history of previous HF hospitalization. In the patients in NYHA class I, MADIT-CRT did not show significant reduction in the all-cause mortality or HF event rate by CRT over ICD. In REVERSE, a trend was observed toward less clinical efficacy conferred by CRT among class I as compared with class II patients. There is no convincing evidence that CRT is indicated in patients presenting with no or transient, mild symptoms and the recommendation is restricted to patients in NYHA II.

Device selection

There are arguments in favour of a preferential implantation of CRT-D in this less severely ill patient population. First, the randomized trials have predominantly or exclusively implanted CRT-D instead of CRT-P²⁵ (Tables 1 and 2). Consequently, there is no solid evidence currently supporting the use of CRT-P in this population. Second, the significantly younger age, lower comorbidity and longer life expectancy of patients presenting in NYHA class I or II compared with class III or IV may support the use of CRT-D; but other arguments may plead for not excluding CRT-P. First, as a survival advantage was not shown^{19,20} the clinical benefit conferred by device therapy in NYHA class I/II patients is probably attributable to cardiac resynchronization through reverse LV remodelling. This benefit was equal for CRT-P and CRT-D^{10,11} in NYHA class III/IV. Second, due to the remodelling process, many class I/II patients may see their LVEF increase to $>35\%$ (the threshold value for ICD indication in HF) after 6–12 months of CRT. Third, CRT-D seems to be associated with a higher risk of device-related complications as compared with CRT-P.²⁶ The relative risk–benefit

advantage of CRT-D over CRT-P remains unclear, especially in this population with milder symptoms.

Key points

- Two recent, randomized, prospective, multicentre trials in mild HF (MADIT-CRT and REVERSE) demonstrated reduced morbidity.
- 18% of patients in REVERSE and 15% of patients in MADIT-CRT were in NYHA I class at baseline although most of these patients had been previously symptomatic.
- Improvement was primarily seen in patients with QRS ≥ 150 ms and/or typical LBBB.
- In MADIT-CRT, women with LBBB demonstrated a particularly favourable response.
- Survival advantage is not established.
- In MADIT-CRT the extent of reverse remodelling was concordant with and predictive of improvement in clinical outcomes.

4. Cardiac resynchronization therapy with pacemaker/defibrillator function in patients with heart failure and permanent atrial fibrillation

Randomized studies of CRT to date have been almost exclusively restricted to patients in SR. This contrasts with the high prevalence of CRT use in routine practice as indicated by the recent ESC CRT survey,²⁷ thus indicating a need for prospective controlled trials. Approximately one-fifth of patients receiving CRTs in Europe have permanent atrial fibrillation (AF). The prevalence of AF in patients with HF is linked to the severity of the disease: 5% in NYHA I as compared with 25–50% in NYHA III/IV patients.^{28,29} Patients suffering from AF and ventricular dyssynchrony are typically older, and have a higher prevalence of comorbidity and a worse prognosis than patients in SR.^{27,30–32} It should be emphasized that patients with symptomatic HF, AF, and an LVEF of $\leq 35\%$ may satisfy the criteria for ICD implantation. The presence of QRS prolongation would favour implantation of a CRT-D in these patients. In that the evidence is limited in AF and most of the patients included in trials had a very wide QRS width, we restrict our recommendation for CRT-P/CRT-D to QRS ≥ 130 ms.

Some patients with permanent AF may resume SR during long-term treatment or following successful left atrial ablation.^{33,34} No comparative data exist on the efficacy of rhythm versus rate control strategy in patients with either paroxysmal/persistent or permanent AF, HF, and QRS duration ≥ 120 ms. Current knowledge restricts us to the use of rate control strategy in the subgroup of patients with permanent AF. In this latter group of patients outcomes are more difficult to measure, since both heart rate control and CRT may contribute to the observed changes in clinical status.³⁵ An adequate trial with pharmacologically induced rate control is advisable. However, there is consensus that essentially complete ventricular capture is mandatory in order to maximize clinical benefit and improve the prognosis of patients with permanent AF.³⁶ This often requires creation of complete heart block by ablation of the AV junction given the frequently inadequate efficacy of pharmacological

Recommendation in patients with heart failure in New York Heart Association function class II

Recommendation	Patient population	Class ^a	Level ^b	Ref. ^c
CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression ^d	NYHA function class II LVEF ≤35%, QRS ≥150 ms, SR Optimal medical therapy	I	A	9, 20–22

^aClass of recommendation.

^bLevel of evidence.

^cReferences.

^dThe guideline indication has been restricted to patients with HF in NYHA function class II with a QRS width ≥ 150 ms, a population with a high likelihood of a favourable response. CRT = cardiac resynchronization therapy; CRT-D = CRT with defibrillator function; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

treatment of ventricular rate control at rest and during exercise. Frequent pacing is defined as ≥95% pacemaker dependency.³⁷

Since the publication of the previous versions of guidelines on CRT, mortality data from a large prospectively designed registry including AF patients³⁰ and several small observational studies^{38,39} in addition to a meta-analysis have been published.⁴⁰ The majority of patients in this meta-analysis had undergone AV nodal ablation. A large, prospective, observational registry³³ showed that, during long-term follow-up, hybrid therapy combining CRT with AV ablation (resulting in 100% effective biventricular stimulation) conferred improvements in LV function and exercise capacity comparable to those achieved in patients with SR. In the same cohort,²⁸ the authors provided evidence that patients with HF and AF treated with CRT received the same survival benefit as those achieved in patients with SR only when AV

ablation was performed shortly after CRT implantation. These observational data need to be confirmed in randomized controlled studies in the cohort of patients with HF and permanent AF.

Key points

- Approximately one-fifth of CRT implantations in Europe are in patients with permanent AF.
- NYHA class III/IV symptoms and an LVEF of ≤35% are well-established indications for ICD.
- Frequent pacing is defined as ≥95% pacemaker dependency.³⁷
- AV nodal ablation may be required to assure adequate pacing.
- Evidence is strongest for patients with an LBBB pattern.
- Insufficient evidence for mortality recommendation.

Recommendations in patients with heart failure and permanent atrial fibrillation

Recommendations	Patient population	Class ^a	Level ^b	Ref. ^c
CRT-P/CRT-D ^d should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥130 ms Pacemaker dependency induced by AV nodal ablation	IIa	B	27–40
CRT-P/CRT-D ^d should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥130 ms Slow ventricular rate and frequent pacing ^e	IIa	C	—

^aClass of recommendation.

^bLevel of evidence.

^cReferences.

^dReasonable expectation of survival with good functional status for >1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.

^eFrequent pacing is defined as ≥95% pacemaker dependence.

CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

Recommendations in patients with heart failure and a concomitant class I pacemaker indication

Recommendations	Patient population	Class ^a	Level ^b	Ref. ^c
CRT-P/CRT-D ^d is recommended to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms	I	B	41–48
CRT-P/CRT-D ^d should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS <120 ms	IIa	C	—
CRT-P/CRT-D ^d may be considered to reduce morbidity	NYHA function class II LVEF ≤35%, QRS <120 ms	IIb	C	—

^aClass of recommendation.

^bLevel of evidence.

^cReferences.

^dReasonable expectation of survival with good functional status for >1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D. CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

5. Cardiac resynchronization therapy with pacemaker/defibrillator function in patients with heart failure and a conventional pacemaker indication

Although prospective randomized controlled studies specifically addressing the issue of CRT in patients with a narrow QRS complex are currently lacking, there are several retrospective observational series or small prospective trials demonstrating a clinical benefit of upgrading to biventricular pacing with long-standing right ventricular pacing, severe ventricular dysfunction, NYHA function class III symptoms, regardless of QRS duration.^{41–46} This may indirectly indicate that preservation and/or restoration of an intrinsic, near-normal activation sequence by biventricular pacing should be pursued regardless of rhythm.

It is important to distinguish which part of the clinical picture may be secondary to the underlying bradyarrhythmia rather than LV dysfunction. Once severe reduction of functional capacity as well as LV dysfunction have been confirmed, then it is reasonable to consider biventricular pacing for the improvement of symptoms. Conversely, the detrimental effects of right ventricular pacing on symptoms and LV function in patients with HF of ischaemic origin and preserved LVEF have been demonstrated.⁴⁷ The underlying rationale of recommending biventricular pacing should therefore aim to avoid chronic right ventricular pacing in HF patients who already have LV dysfunction.⁴⁸

Initiation and up-titration of β -blocker treatment, indicated in patients with symptomatic HF, may reduce heart rate and increase pacemaker dependency. Patients with a CRT-P/CRT-D will better tolerate increased pacing time. This may permit initiation of β -blocking treatment or dosage increase in those patients who are already on therapy, confirming a frequently reported clinical observation of dosage up-titration in HF patients treated with CRT.

Recommendation in patients with severe heart failure ineligible for transplant

Recommendations	Patient population	Class ^a	Level ^b	Ref. ^c
LVAD may be considered as destination treatment to reduce mortality	NYHA function class IIIB/IV LVEF ≤25% peak VO ₂ <14 mL/kg/min ^d	IIb	B	49–53

^aClass of recommendation.

^bLevel of evidence.

^cReferences.

^dIf obtainable.

LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Key points

- In patients with a conventional indication for pacing, NYHA III/IV symptoms, an LVEF of $\leq 35\%$, and a QRS width of ≥ 120 ms, a CRT-P/CRT-D is indicated.
- RV pacing will induce dyssynchrony.
- Chronic RV pacing in patients with LV dysfunction should be avoided.
- CRT may permit adequate up-titration of β -blocker treatment.

6. Left ventricular assist device as destination therapy for patients with severe heart failure ineligible for cardiac transplantation

Patients with end-stage HF have a poor quality of life, a very high mortality rate, and are potential candidates for implantation of a left ventricular assist device (LVAD). Although cardiac transplantation (CTX) is associated with high 1- and 10-year survival rates, organ supply is limited. The technical improvements and proven success of implantable LVADs have made it a reasonable treatment option in these patients, either as a bridge to CTX or as destination therapy. Patient selection for LVAD is crucial. Most patients are on continuous inotropic support. Patients with severe renal, pulmonary, or hepatic dysfunction as well as patients with active infection or cardiogenic shock should not be considered as candidates.⁴⁹

One recent study was conducted in 200 patients as destination therapy, who were randomized in a 2:1 ratio to a continuous-flow device (HeartMate II) or a pulsatile device.⁵⁰ Patients were in NYHA function class III/IV with an LVEF of $\leq 25\%$. A peak VO_2 of ≤ 14 mL/kg/min was an inclusion criterion in HeartMate II but

gas-exchange data during exercise is not routinely available in clinical practice and may be inconclusive. The primary composite endpoint was, at 2 years, freedom from disabling stroke or reoperation to repair or replace the device. Secondary endpoints included actuarial survival; mean age of the patients was 64 years, and the mean LVEF was 17%. The primary endpoint was achieved in more patients with the continuous-flow device (46 vs. 11%, $P < 0.001$) and actuarial survival at 2 years was higher (58 vs. 24%, $P = 0.008$). Another recent (uncontrolled) study examined 281 patients in whom the continuous device was implanted as bridge to CTX.⁵¹ After 18 months, 222 patients (79%) underwent CTX, LVAD removal for cardiac recovery, or required ongoing LVAD support.⁵² The INTERMACS registry, an National Institutes of Health (NIH)-supported initiative, demonstrates that in practice $\sim 10\%$ of patients receiving an LVAD are not considered candidates for CTX at the time of implantation.⁵³

Key points

- Data from the NIH-supported INTERMACS registry indicates that $\sim 10\%$ of patients in clinical practice receive an LVAD as destination therapy.
- Patient population consists mainly of patients on inotropic (and/or mechanical) support prior to LVAD implantation.
- Patient selection is crucial and candidates should not have significant renal, pulmonary, or hepatic dysfunction or infection.
- The available evidence suggests that a continuous flow device is superior to a pulsatile flow device.
- No controlled data available as bridge to CTX.

7. Evidence tables

Table 1 Inclusion criteria in randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial	Patients	NYHA class	LVEF (%)	LVEDD (mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR ¹⁶	58	III	≤ 35	≥ 60	SR	≥ 150	No
MIRACLE ⁵	453	III, IV	≤ 35	≥ 55	SR	≥ 130	No
MUSTIC AF ³⁵	43	III	≤ 35	≥ 60	AF	≥ 200	No
PATH CHF ⁶	41	III, IV	≤ 35	NA	SR	≥ 120	No
MIRACLE ICD ⁸	369	III, IV	≤ 35	≥ 55	SR	≥ 130	Yes
CONTAK CD ⁵⁴	227	II, IV	≤ 35	NA	SR	≥ 120	Yes
MIRACLE ICD II ⁹	186	II	≤ 35	≥ 55	SR	≥ 130	Yes
PATH CHF II ⁵⁵	89	III, IV	≤ 35	NA	SR	≥ 120	Yes/no
COMPANION ¹⁰	1520	III, IV	≤ 35	NA	SR	≥ 120	Yes/no
CARE HF ¹¹	814	III, IV	≤ 35	≥ 30	SR	≥ 120	No
CARE HF ¹⁷	813	III, IV	≤ 35	≥ 30	SR	≥ 120	No
REVERSE ^{21,22}	610	I, II	≤ 40	≥ 55	SR	≥ 120	Yes/no
MADIT CRT ²⁰	1800	I, II	≤ 30	NA	SR	≥ 130	Yes
RAFT ⁵⁶	1800 Canada	II, III	≤ 30	> 60	SR/AF	≥ 130 $\geq 200^a$	Yes

^aPatients in AF.

AF = atrial fibrillation; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NA = not applicable; NYHA = New York Heart Association; SR = sinus rhythm.

Table 2 Endpoints, design, and main findings of the randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial	Endpoints	Design	Main findings
MUSTIC-SR ¹⁶	6MWT, QoL, pVO ₂ , Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved: 6MWT, QoL, pVO ₂ ; reduced Hosp
MIRACLE ⁸	NYHA class, QoL, pVO ₂	Double-blinded, controlled, 6 months	CRT-P improved: NYHA, pVO ₂ , 6MWT
MUSTIC AF ³⁵	6MWT, QoL, pVO ₂ , Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved all; reduction of Hosp
PATH CHF ⁶	6MWT, pVO ₂	Single-blinded, controlled, crossover, 12 months	CRT-P improved: 6MWT; pVO ₂
MIRACLE ICD ⁸	6MWT, QoL, Hosp	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved all from baseline (not ICD)
CONTAK CD ⁵⁴	All-cause death + HF Hosp, pVO ₂ , 6MWT, NYHA class, QoL, LVEDD, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: pVO ₂ , 6MWT; reduced LVEDD and increased LVEF
MIRACLE ICD II ⁹	VE/CO ₂ , pVO ₂ , NYHA, QoL, 6MWT, LV volumes, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: NYHA, VE/CO ₂ ; volumes, LVEF
COMPANION ¹⁰	(i) All-cause death or Hosp	Double-blinded, controlled, OMT, CRT-D, CRT-P, ~15 months	CRT-P/CRT-D: reduced (i)
CARE-HF ¹¹	(i) All-cause death or CV event (ii) All-cause death	Double-blinded, controlled, OMT, CRT-P, 29 months	CRT-P reduced (i) and (ii)
REVERSE ²¹	(i) % worsened by clinical composite endpoint, (ii) LVESVi, (iii) HF Hosp, (iv) all-cause death	Double-blinded, controlled, OMT, CRT-P ± ICD, 12 months	Primary endpoint NS; CRT-P/CRT-D reduced (ii) and (iii) Hosp but not (iv)
MADIT-CRT ²⁰	(i) HF event or death, (ii) All-cause death, (iii) LVESV	Controlled, CRTP, CRT-D, 2.4 years	CRT-D reduced (i) and (iii) but not (ii)

AF = atrial fibrillation; CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; CV = cardiovascular; HF = heart failure; Hosp = hospitalization; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESi = left ventricular stroke volume index, LVESV = left ventricular end-systolic volume; 6MWT = 6 min walk test; NYHA = New York Heart Association; NS = not significant; OMT = optimal medical therapy; pVO₂ = peak oxygen consumption; QoL = quality of life; SR = sinus rhythm; VE/CO₂ = ventilation/carbon dioxide ratio.

References

- Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Piori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. 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**:2388–2442.
- Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluzka M, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Piori SG, Blomström-Lundqvist C, Brignole M, Terradellas JB, Camm J, Castellano P, Cleland J, Farre J, Fromer M, Le Heuzey JY, Lip GY, Merino JL, Montenero AS, Ritter P, Schalij MJ, Stellbrink C. Guidelines for cardiac pacing and cardiac resynchronization therapy: the Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J* 2007;**28**:2256–2295.
- Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail* 2002;**4**:361–371.
- van Veldhuisen DJ, Maass AH, Piori SG, Stolt P, van Gelder IC, Dickstein K, Swedberg K. Implementation of device therapy (cardiac resynchronization therapy and implantable cardioverter defibrillator) for patients with heart failure in Europe: changes from 2004 to 2008. *Eur J Heart Fail* 2009;**11**:1143–1151.
- Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
- Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schöndube F, Wolfhard U, Bocker D, Krahnfeld O, Kirkels H. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;**39**:2026–2033.
- Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, Yong PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;**42**:1454–1459.
- Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. *JAMA* 2003;**289**:2685–2694.
- Abraham WT, Young JB, Leon AR, Adler S, Bank AJ, Hall SA, Lieberman R, Liem LB, O'Connell JB, Schroeder JS, Wheelan KR. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;**110**:2864–2868.
- Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
- Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2006;**27**:2682–2688.
- Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, Kass DA, Powe NR. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;**289**:730–740.
- McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, Hartling L, Klassen T, Abraham W. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med* 2004;**141**:381–390.
- Lam SK, Owen A. Combined resynchronization and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomized controlled trials. *Br Med J* 2007;**335**:925.
- Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, McKenna W, Fitzgerald M, Deharo JC, Alonso C, Walker S, Braunschweig F, Bailleul C, Daubert JC. Long-term benefits of biventricular pacing in congestive heart failure: results from the MULTISite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;**40**:111–118.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CARDiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;**27**:1928–1932.
- Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, Freemantle N, Cleland JG, Tavazzi L, Daubert C. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail* 2009;**11**:699–705.
- Lindenfeld J, Feldman AM, Saxon L, Boehmer J, Carson P, Ghali JK, Anand I, Singh S, Steinberg JS, Jaski B, DeMarco T, Mann D, Yong P, Galle E, Ecklund F, Bristow M. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. *Circulation* 2007;**115**:204–212.
- Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
- Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. 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**:1834–1843.
- Daubert JC, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Torok T, Linde C. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol* 2009;**54**:1837–1846.
- Linde C, Gold M, Abraham WT, Daubert JC. Rationale and design of a randomized controlled trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with asymptomatic left ventricular dysfunction with previous symptoms or mild heart failure—the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Am Heart J* 2006;**151**:288–294.
- Solomon SDF, Bourgon E, Shah M, Brown M, Hall WJ, Pfeffer MA, Moss AJ. Effect of Cardiac Resynchronization Therapy on Reverse Remodeling and Relation to Outcome: MADIT-CRT. *Circulation* 2010 10.1161/CIRCULATIONAHA.110.955039.
- Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
- Romeyer-Bouchard C, Da Costa A, Dauphinot V, Messier M, Bisch L, Samuel B, Lafond P, Ricci P, Isaaq K. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. *Eur Heart J* 2010;**31**:203–210.
- Dickstein K, Bogale N, Piori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J. The European cardiac resynchronization therapy survey. *Eur Heart J* 2009;**30**:2450–2460.
- Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, Curnis A, Vogt J, Klersy C. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. *Eur Heart J* 2008;**29**:1644–1652.
- Neuberger HR, Mewis C, van Veldhuisen DJ, Schotten U, van Gelder IC, Allessie MA, Bohm M. Management of atrial fibrillation in patients with heart failure. *Eur Heart J* 2007;**28**:2568–2577.
- Daubert JC. Introduction to atrial fibrillation and heart failure: a mutually noxious association. *Europace* 2004;**5** Suppl 1:S1–S4.
- Baldasseroni S, De Biase L, Fresco C, Marchionni N, Marini M, Masotti G, Orsini G, Porcu M, Pozzar F, Scherillo M, Maggioni AP. Cumulative effect of complete left bundle-branch block and chronic atrial fibrillation on 1-year mortality and hospitalization in patients with congestive heart failure. A report from the Italian network on congestive heart failure (in-CHF database). *Eur Heart J* 2002;**23**:1692–1698.
- Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, Campana C, Perini G, Deorsola A, Masotti G, Tavazzi L, Maggioni AP. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J* 2002;**143**:398–405.
- Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, Ceriotti C, Gronda E, Klersy C, Frattini S, Klein HH. Four-year efficacy of cardiac

- resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2006;**48**:734–743.
34. Gasparini M, Steinberg JS, Arshad A, Regoli F, Galimberti P, Rosier A, Daubert JC, Klersy C, Kamath G, Leclercq C. Resumption of sinus rhythm in patients with heart failure and permanent atrial fibrillation undergoing cardiac resynchronization therapy: a longitudinal observational study. *Eur Heart J* 2010;**31**:976–983.
 35. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, Djiane P, Mabo P, Levy T, Gadler F, Bailleul C, Daubert JC. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;**23**:1780–1787.
 36. Ferreira AM, Adragao P, Cavaco DM, Candeias R, Morgado FB, Santos KR, Santos E, Silva JA. Benefit of cardiac resynchronization therapy in atrial fibrillation patients vs. patients in sinus rhythm: the role of atrioventricular junction ablation. *Europace* 2008;**10**:809–815.
 37. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? *J Am Coll Cardiol* 2009;**53**:355–360.
 38. Khadjooi K, Foley PW, Chalil S, Anthony J, Smith RE, Frenneaux MP, Leyva F. Long-term effects of cardiac resynchronization therapy in patients with atrial fibrillation. *Heart* 2008;**94**:879–883.
 39. Delnoy PP, Ottervanger JP, Luttkhuis HO, Elvan A, Misier AR, Beukema WP, van Hemel NM. Comparison of usefulness of cardiac resynchronization therapy in patients with atrial fibrillation and heart failure versus patients with sinus rhythm and heart failure. *Am J Cardiol* 2007;**99**:1252–1257.
 40. Upadhyay GA, Choudhry NK, Auricchio A, Ruskin J, Singh JP. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2008;**52**:1239–1246.
 41. Bleeker GB, Holman ER, Steendijk P, Boersma E, van der Wall EE, Schalij MJ, Bax JJ. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol* 2006;**48**:2243–2250.
 42. Vatankulu MA, Goktekin O, Kaya MG, Ayhan S, Kucukdurmaz Z, Sutton R, Henein M. Effect of long-term resynchronization therapy on left ventricular remodeling in pacemaker patients upgraded to biventricular devices. *Am J Cardiol* 2009;**103**:1280–1284.
 43. Paparella G, Sciarra L, Capulzini L, Francesconi A, De Asmundis C, Sarkozy A, Cazzin R, Brugada P. Long-term effects of upgrading to biventricular pacing: differences with cardiac resynchronization therapy as primary indication. *Pacing Clin Electrophysiol* 2010;**33**:841–849.
 44. van Geldorp IE, Vernooy K, Delhaas T, Prins MH, Crijns HJ, Prinzen FW, Dijkman B. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. *Europace* 2010;**12**:223–229.
 45. van Bommel RJ, Gorcsan J 3rd, Chung ES, Abraham WT, Gjestvang FT, Leclercq C, Monaghan MJ, Nihoyannopoulos P, Peraldo C, Yu CM, Demas M, Gerritse B, Bax JJ. Effects of cardiac resynchronization therapy in patients with heart failure having a narrow QRS complex enrolled in PROSPECT. *Heart* 2010;**96**:1107–1113.
 46. Wein S, Voskoboinik A, Wein L, Billah B, Krum H. Extending the boundaries of cardiac resynchronization therapy: efficacy in atrial fibrillation, New York Heart Association class II, and narrow QRS heart failure patients. *J Card Fail* 2010;**16**:432–438.
 47. Yu CM, Chan JY, Zhang Q, Omar R, Yip GW, Hussin A, Fang F, Lam KH, Chan HC, Fung JW. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med* 2009;**361**:2123–2134.
 48. Kindermann M, Hennen B, Jung J, Geisel J, Bohm M, Frohlig G. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol* 2006;**47**:1927–1937.
 49. Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. *Eur J Heart Fail* 2010;**12**:434–443.
 50. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;**361**:2241–2251.
 51. Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, Conte JV, Bogaev RC, MacGillivray TE, Naka Y, Mancini D, Massey HT, Chen L, Klodell CT, Aranda JM, Moazami N, Ewald GA, Farrar DJ, Frazier OH. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol* 2009;**54**:312–321.
 52. Drews T, Stepanenko A, Dandel M, Buz S, Lehmkühl HB, Hetzer R. Mechanical circulatory support in patients of advanced age. *Eur J Heart Fail* 2010; May 22 [epub ahead of print] doi: 10.1093/eurjhf/hfq076.
 53. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Ullisney KL, Baldwin JT, Young JB. Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. *J Heart Lung Transplant* 2010;**29**:1–10.
 54. Achtelek M, Bocchiardo M, Trappe HJ, Gaita F, Lozano I, Niazi I, Gold M, Yong P, Duby C. Performance of a new steroid-eluting coronary sinus lead designed for left ventricular pacing. *Pacing Clin Electrophysiol* 2000;**23**:1741–1743.
 55. Stellbrink C, Auricchio A, Butter C, Sack S, Vogt J, Bocker D, Block M, Kirkels H, Ramdat-Misier A. Pacing Therapies in Congestive Heart Failure II study. *Am J Cardiol* 2000;**86**:138K–143K.
 56. Tang AS, Wells GA, Arnold M, Connolly S, Hohnloser S, Nichol G, Rouleau J, Sheldon R, Talajic M. Resynchronization/defibrillation for ambulatory heart failure trial: rationale and trial design. *Curr Opin Cardiol* 2009;**24**:1–8.