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

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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) guidelines were published in 2008 and the cardiac pacing guidelines in 2007. 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. The initial expense of device implantation must be weighed against measures of short- and long-term efficacy with...
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.⁹,¹⁶,¹⁷

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.⁴,¹⁰,¹¹ 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 prespecified 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 ≤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.
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. 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. 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-CRT and REVERSE, 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 I.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 REVERSE21,22 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 towards 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-D10,11 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 < 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
treatment of ventricular rate control at rest and during exercise. Frequent pacing is defined as $\geq 95\%$ pacemaker dependency.\textsuperscript{37}

Since the publication of the previous versions of guidelines on CRT, mortality data from a large prospectively designed registry including AF patients\textsuperscript{30} and several small observational studies\textsuperscript{38,39} in addition to a meta-analysis have been published.\textsuperscript{40} The majority of patients in this meta-analysis had undergone AV nodal ablation. A large, prospective, observational registry,\textsuperscript{13} 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,\textsuperscript{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 $\leq 35\%$ are well-established indications for ICD.
- Frequent pacing is defined as $\geq 95\%$ pacemaker dependency.\textsuperscript{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 in New York Heart Association function class II

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient population</th>
<th>Class$^a$</th>
<th>Level$^b$</th>
<th>Ref.$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression$^d$</td>
<td>NYHA function class II LVEF $\leq 35%$, QRS $\geq 150$ ms, SR</td>
<td>I</td>
<td>A</td>
<td>9, 20–22</td>
</tr>
<tr>
<td>CRT preferentially by CRT-D should be considered to reduce morbidity</td>
<td>Optimal medical therapy</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a$Class of recommendation.
$^b$Level of evidence.
$^c$References.
$^d$Reasonable 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.

### Recommendations in patients with heart failure and permanent atrial fibrillation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Patient population</th>
<th>Class$^a$</th>
<th>Level$^b$</th>
<th>Ref.$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D$^d$ should be considered to reduce morbidity</td>
<td>NYHA function class III/IV LVEF $\leq 35%$, QRS $\geq 130$ ms Pacemaker dependency induced by AV nodal ablation</td>
<td>IIA</td>
<td>B</td>
<td>27–40</td>
</tr>
<tr>
<td>CRT-P/CRT-D$^d$ should be considered to reduce morbidity</td>
<td>NYHA function class III/IV LVEF $\leq 35%$, QRS $\geq 130$ ms Slow ventricular rate and frequent pacing$^e$</td>
<td>IIA</td>
<td>C</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a$Class of recommendation.
$^b$Level of evidence.
$^c$References.
$^d$Frequent pacing is defined as $\geq 95\%$ pacemaker dependency.

$^e$Frequent pacing is defined as $\geq 95\%$ pacemaker dependency.

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.

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

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

\(^a\)Class of recommendation.  
\(^b\)Level of evidence.  
\(^c\)References.  
\(^d\)Reasonable 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.

### Recommendations in patients with severe heart failure ineligible for transplant

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Patient population</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVAD may be considered as destination treatment to reduce mortality</td>
<td>NYHA function class IIIb/IV LVEF ≤25% peak VO(_2) ≤14 mL/kg/min(^d)</td>
<td>IIb</td>
<td>B</td>
<td>49–53</td>
</tr>
</tbody>
</table>

\(^a\)Class of recommendation.  
\(^b\)Level of evidence.  
\(^c\)References.  
\(^d\)If 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 ≤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.

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. Patients in NYHA function class IIIB/IV with an LVEF of <35%, and a QRS width of ≥120 ms, a peak VO₂ 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. After 18 months, 222 patients (79%) underwent CTX, LVAD removal for cardiac recovery, or required ongoing LVAD support. The INTERMACS registry, an National Institutes of Health (NIH)-supported initiative, demonstrates that in practice ~10% of patients receiving an LVAD are not considered candidates for CTX at the time of implantation.

Key points

- Data from the NIH-supported INTERMACS registry indicates that ~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>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>NYHA class</th>
<th>LVEF (%)</th>
<th>LVEDD (mm)</th>
<th>SR/AF</th>
<th>QRS (ms)</th>
<th>ICD</th>
</tr>
</thead>
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<tr>
<td>MUSTIC-SR</td>
<td>58</td>
<td>III</td>
<td>≤35</td>
<td>≥60</td>
<td>SR</td>
<td>≥150</td>
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<tr>
<td>MIRACLE</td>
<td>453</td>
<td>III, IV</td>
<td>≤35</td>
<td>≥55</td>
<td>SR</td>
<td>≥130</td>
<td>No</td>
</tr>
<tr>
<td>MUSTIC AF</td>
<td>43</td>
<td>III</td>
<td>≤35</td>
<td>≥60</td>
<td>AF</td>
<td>≥200</td>
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<tr>
<td>PATH CHF</td>
<td>41</td>
<td>III, IV</td>
<td>≤35</td>
<td>NA</td>
<td>SR</td>
<td>≥120</td>
<td>No</td>
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<tr>
<td>MIRACLE ICD</td>
<td>369</td>
<td>III, IV</td>
<td>≤35</td>
<td>≥55</td>
<td>SR</td>
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<td>Yes</td>
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<td>CONTAK CD</td>
<td>227</td>
<td>II, IV</td>
<td>≤35</td>
<td>NA</td>
<td>SR</td>
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<td>Yes</td>
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<td>MIRACLE ICD II</td>
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<td>II</td>
<td>≤35</td>
<td>≥55</td>
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<td>≥130</td>
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<td>PATH CHF II</td>
<td>89</td>
<td>III, IV</td>
<td>≤35</td>
<td>NA</td>
<td>SR</td>
<td>≥120</td>
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<td>COMPANION</td>
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<td>III, IV</td>
<td>≤35</td>
<td>NA</td>
<td>SR</td>
<td>≥120</td>
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<td>CARE HF</td>
<td>814</td>
<td>III, IV</td>
<td>≤35</td>
<td>≥30</td>
<td>SR</td>
<td>≥120</td>
<td>No</td>
</tr>
<tr>
<td>CARE HF II</td>
<td>813</td>
<td>III, IV</td>
<td>≤35</td>
<td>≥30</td>
<td>SR</td>
<td>≥120</td>
<td>No</td>
</tr>
<tr>
<td>REVERSE</td>
<td>610</td>
<td>I, II</td>
<td>≤40</td>
<td>≥55</td>
<td>SR</td>
<td>≥120</td>
<td>Yes/no</td>
</tr>
<tr>
<td>MADIT CRT</td>
<td>1800</td>
<td>I, II</td>
<td>≤30</td>
<td>≥60</td>
<td>SR/AF</td>
<td>≥130</td>
<td>Yes</td>
</tr>
<tr>
<td>RAFT</td>
<td>1800 Canada</td>
<td>II, III</td>
<td>≤30</td>
<td>≥60</td>
<td>SR/AF</td>
<td>≥130</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

*Patients 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Endpoints</th>
<th>Design</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC-SR16</td>
<td>6MWT, QoL, pVO₂, Hosp</td>
<td>Single-blinded, controlled, crossover, 6 months</td>
<td>CRT-P improved: 6MWT, QoL, pVO₂; reduced Hosp</td>
</tr>
<tr>
<td>MIRACLE8</td>
<td>NYHA class, QoL, pVO₂</td>
<td>Double-blinded, controlled, 6 months</td>
<td>CRT-P improved: NYHA, pVO₂, 6MWT</td>
</tr>
<tr>
<td>MUSTIC AF35</td>
<td>6MWT, QoL, pVO₂, Hosp</td>
<td>Single-blinded, controlled, crossover, 6 months</td>
<td>CRT-P improved all; reduction of Hosp</td>
</tr>
<tr>
<td>PATH CHF6</td>
<td>6MWT, pVO₂</td>
<td>Single-blinded, controlled, crossover, 12 months</td>
<td>CRT-P improved: 6MWT; pVO₂</td>
</tr>
<tr>
<td>MIRACLE AF35</td>
<td>6MWT, QoL, Hosp</td>
<td>Double-blinded, ICD vs. CRT-D 6 months</td>
<td>CRT-D improved all from baseline (not ICD)</td>
</tr>
<tr>
<td>CONTAK CD54</td>
<td>All-cause death + HF Hosp, pVO₂, 6MWT, NYHA class, QoL, LVEDD, LVEF</td>
<td>Double-blinded, ICD vs. CRT-D 6 months</td>
<td>CRT-D improved: pVO₂, 6MWT; reduced LVEDD and increased LVEF</td>
</tr>
<tr>
<td>MIRACLE ICD II9</td>
<td>VE/CO₂, pVO₂, NYHA, QoL, 6MWT, LV volumes, LVEF</td>
<td>Double-blinded, ICD vs. CRT-D 6 months</td>
<td>CRT-D improved: NYHA, VE/CO₂; volumes, LVEF</td>
</tr>
<tr>
<td>COMPANION10</td>
<td>(i) All-cause death or Hosp</td>
<td>Double-blinded, controlled, OMT, CRT-D, CRT-P, ~15 months</td>
<td>CRT-P/CRT-D: reduced (i)</td>
</tr>
<tr>
<td>CARE-HF11</td>
<td>(i) All-cause death or CV event</td>
<td>Double-blinded, controlled, OMT, CRT-P, 29 months</td>
<td>CRT-P reduced (i) and (ii)</td>
</tr>
<tr>
<td>REVERSE11</td>
<td>(i) % worsened by clinical composite endpoint, (ii) LVEV, (iii) HF Hosp, (iv) all-cause death</td>
<td>Double-blinded, controlled, OMT, CRT-P + ICD, 12 months</td>
<td>Primary endpoint NS; CRT-P/CRT-D reduced (ii) and (iii) Hosp but not (iv)</td>
</tr>
<tr>
<td>MADIT-CRT20</td>
<td>(i) HF event or death, (ii) All-cause death, (iii) LVESV</td>
<td>Controlled, CRTP, CRT-D, 2.4 years</td>
<td>CRT-D reduced (i) and (ii) but not (i)</td>
</tr>
</tbody>
</table>

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.


