REVIEW ARTICLE

# Which patients with chronic heart failure should be referred for CRT-D implantation?

## Practical implications of current clinical research

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**KEY WORDS**

cardiac resynchronization therapy, cardiomyopathy, heart failure, implantable cardioverter--defibrillator

**ABSTRACT**

Over the last decade, cardiac resynchronization therapy (CRT) has emerged as an important treatment modality in patients with heart failure. Primary prevention of mortality with implantable cardioverter-defibrillator (ICD) in patients with ischemic and nonischemic cardiomyopathy and left ventricular dysfunction (ejection fraction [EF] ≤35%) has become the standard of care. A growing number of patients with indications for ICD are also eligible for CRT, receiving resynchronization pacing-defibrillator devices (CRT-D). Randomized clinical trials have provided evidence that cardiac resynchronization therapy is beneficial in heart failure patients and contributes to a significant decrease in heart failure progression on top of administering optimal pharmacological therapy. Currently approved indications for CRT-D include utilizing this treatment modality in heart failure patients with New York Heart Association (NYHA) class III or IV, EF ≤35%, and QRS ≥120 ms. New data from MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy) document that patients with less advanced heart failure (ischemic cardiomyopathy in NYHA class I or II and nonischemic cardiomyopathy class II), EF ≤30%, and QRS ≥130 ms also benefit from CRT. These findings indicate that a more proactive approach should be considered regarding the management of heart failure patients with less advanced disease to decrease progression of heart failure with CRT-D therapy.

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**Introduction** The Heart Disease and Stroke Statistics 2010 Update from the American Heart Association[1] reported that in 2006, 1 in 8.6 death certificates ( 282,754 deaths) mentioned heart failure, and there were 5,800,000 patients with heart failure in the United States. Heart failure incidence approaches 10 per 1000 population after 65 years of age, and at 40 years of age the lifetime risk of developing heart failure for men and women is 1 in 5. In 2006, there were 523,000 hospital discharges with a diagnosis of heart failure in men and 583,000 in women. These few facts clearly demonstrate that heart failure is a growing problem with an increasing number of patients developing heart failure in aging societies, with rising costs of healthcare management and hospitalizations and a high number of deaths attributed to heart failure and its complications.

Optimal medical treatment of heart failure requires comprehensive management relying on state-of-the-art evidence-based medicine.[2,3] Recommended management of heart failure should be pertinent to the stage (advancement) of heart failure and its etiology, and it should include life-style modifications, drugs, and devices.[2] Recently, McMurray[3] published a very elegant summary regarding systolic heart failure, and the diagram from this paper provides the currently recommended algorithm for treating patients with systolic heart failure (FIGURE 1).

Apart from optimal medical therapy with diuretics, angiotensin-converting enzyme inhibitors, and β-blockers each patient with an ejection fraction (EF) ≤35% should be considered for implantable cardioverter-defibrillator (ICD) following approved guidelines which are based on

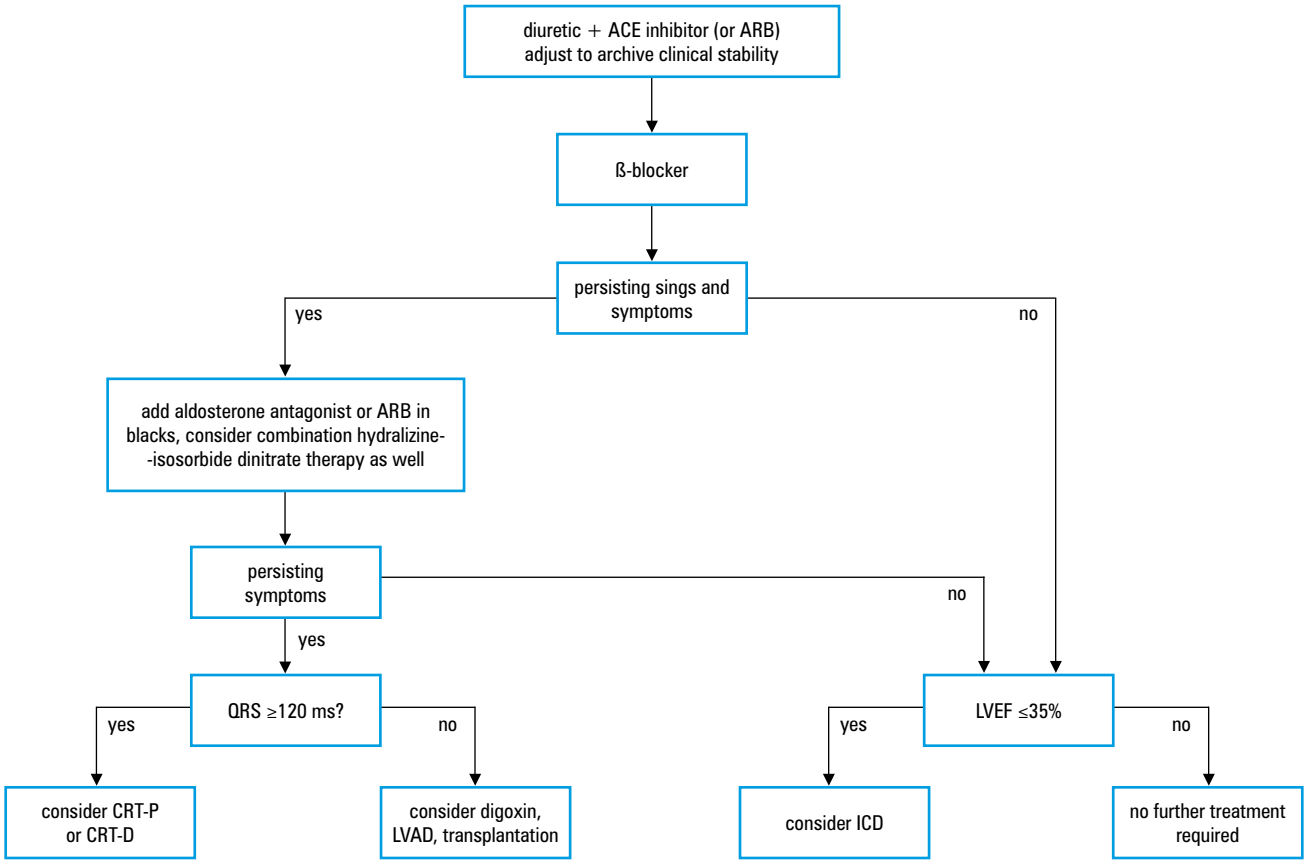


**FIGURE 1** Treatment algorithm for systolic heart failure.[3] (Copyright © 2010 Massachusetts Medical Society. All rights reserved). Abbreviations: ACE – angiotensin-converting enzyme, ARB – angiotensin receptor blocker, CRT-D – cardiac resynchronization therapy defribrillator, CRT-P – CRT pacemaker, ICD – implantable cardioverter-defibrillator, LVAD – left ventricle assist device, LVEF – left ventricular ejection fraction

the results of 2 trials – MADIT II (Multicenter Automatic Defibrillator Implantation Trial II)[4] and SCD-HeFT (Sudden Cardiac Death in Heart Failure).[5] Patients with symptomatic heart failure (class III and IV), EF ≤35%, and QRS ≥120 ms should be offered cardiac resynchronization therapy (CRT), which in combination with ICD (CRT-D) provides both treatment of heart failure and protection from sudden death.

The concept of CRT was invented (patented in 1990) by Drs. Morton Mower and Mieczyslaw Mirowski, who were also the inventors of the ICD.[6] CRT consists of atrial-synchronized pacing of the left ventricle (LV) by an electrode usually placed via the coronary sinus (sometimes applied epicardialy) in order to achieve a more synchronous contraction of the dysfunctional LV.[7-10] Heart failure patients frequently present with depressed LV function and with abnormal asynchronous contractility manifested as a lack of simultaneous contraction of different parts of the ventricular wall (e.g., free wall and septum). This dyssynchrony of contractile function is particularly frequently present in patients with a wide QRS complex and intraventricular conduction abnormalities (predominantly left bundle branch blocks) and it contributes to less effective hemodynamic function of the LV, thus compromising cardiac output and worsening conditions leading to progression of heart failure signs and symptoms. Intraventricular conduction abnormalities also contribute to decreased coordination of the contractile function between the right and left ventricle, and applying pacing to the LV provides an opportunity to more effectively control the simultaneous function of both ventricles. CRT provides an early electrical activation of LV muscle, decreases dyssynchrony of the LV, and leads to hemodynamic improvement in systolic and diastolic function of the LV, while also off-loading the right ventricle.

**Early clinical trials evaluating cardiac resynchronization therapy** Over the last decade, several clinical trials have been conducted examining the role of CRT in the management of patients with heart failure.[11-16] The majority of studies focused on advanced heart failure patients in New York Heart Association (NYHA) class III with a wide QRS complex (≥120 ms). The first randomized clinical trials were small in size and were not able to determine clinical benefits measured by heart failure hospitalization or death. They examined quality of life, patient performance measured by the 6-minute walk test, and echocardiographic parameters reflecting volume and function of the LV.[11-14] In the first landmark study published in 2001, the MUSTIC (Multisite Stimulation in Cardiomyopathies), Cazeau et al.[11] demonstrated in a cross-over design trial that CRT was associated with a significant improvement in the quality of life and 6-minute walk test in 67 patients with NYHA III, wide QRS complex, and EF <35%.

In 2002, Abraham et al.[12] published the results of the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial, in which 453

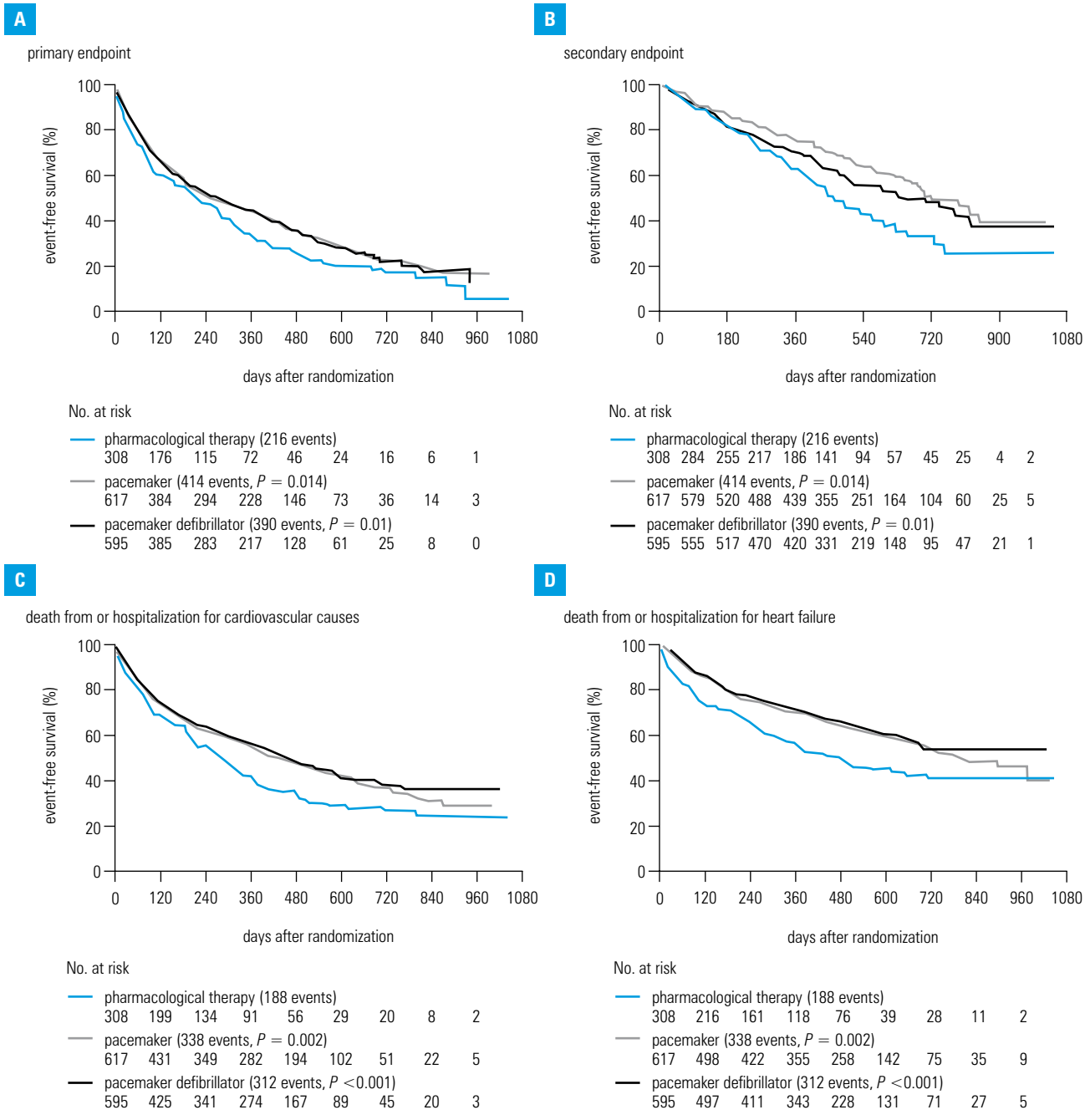


**FIGURE 2** Kaplan-Meier estimates of the time to the primary endpoint of death from or hospitalization for any cause (panel A), the time to the secondary endpoint of death from any cause (panel B), the time to death from or hospitalization for cardiovascular causes (panel C), and the time to death from or hospitalization for heart failure (panel D) in the COMPANION trial.[15] (Copyright © 2010 Massachusetts Medical Society. All rights reserved).

patients with class III heart failure, EF ≤35%, and QRS ≥130 ms were randomly assigned to CRT or to a control group. The primary endpoints were NYHA class, quality of life, and the distance walked in 6 min. As compared with the control group, patients assigned to CRT showed significant improvement in the distance walked in 6 min (+39 vs. +10 m, $P$ = 0.005), functional class ($P$ <0.001), quality of life (–18 vs. –9 points, $P$ = 0.001), time on the treadmill during exercise testing (+81 vs. +19 sec, $P$ = 0.001), EF (+4.6% vs. –0.2%, $P$ <0.001), as well as fewer patients required hospitalization (8% vs. 15%, $P$ <0.05).

In the above trials, CRT was applied without concomitant protection by features of an ICD. Meantime, 2 other clinical trials were conducted that tested the concept of implementing a device which combined CRT and ICD therapy, the so called CRT-D device. In 2003, Higgins et al.[13] published results of the CONTAK CD trial, in which 490 patients were randomized to CRT-D or no-CRT-D for up to 6 months. The use of CRT-D significantly improved peak VO2 (0.8 ml/kg/min vs. 00 ml/kg/min, $P$ = 0.03) and 6-minute walk distance (35 m vs. 15 m, $P$ = 0.043) and was associated with significant reductions in ventricular dimensions and improvement in LVEF (5.1%

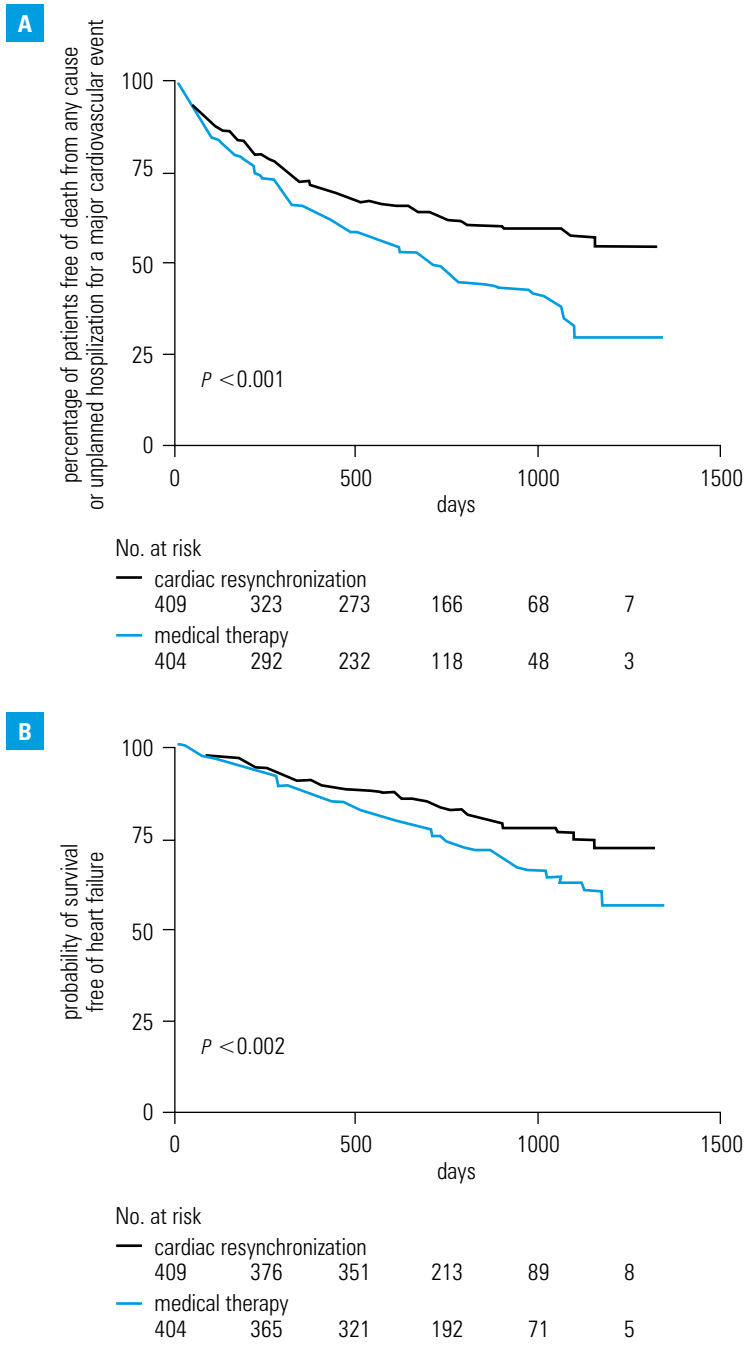


**FIGURE 3** Kaplan-Meier estimates of the time to the primary endpoint of death or hospitalization for cardiovascular event (panel A) and death (panel B) in the CARE-HF trial.[16] (Copyright © 2010 Massachusetts Medical Society. All rights reserved).

vs. 2.8%, $P = 0.02$). However, the frequency of primary endpoints consisting of hospitalization for heart failure, ventricular tachycardia or ventricular fibrillation requiring ICD therapy, or death was not significantly different between groups, not surprisingly since the study was not large enough and with too short a follow-up. Importantly, the study showed feasibility and safety of combined CRT and ICD therapy and significant functional improvements associated with CRT.

In the MIRACLE ICD trial (Multicenter InSync ICD Randomized Clinical Evaluation),[14] 369 patients received CRT-D devices and were randomized to have CRT off or on. At 6 months, patients assigned to CRT had a greater improvement in median quality of life score (–17.5 vs. –11.0, $P = 0.02$) and functional class (–1 vs. 0, $P = 0.007$) than controls but were no different in the change in distance walked in 6 minutes (55 m vs. 53 m, $P = 0.36$). Peak oxygen consumption increased by 1.1 ml/kg per minute in the CRT group vs. 0.1 ml/kg per minute in controls ($P = 0.04$), although treadmill exercise duration increased by 56 sec in the CRT group and decreased by 11 sec in controls ($P < 0.001$). No significant differences were observed in changes in LV size or function, overall heart failure status, survival, and rates of hospitalization.

**Cardiac resynchronization therapy and heart failure hospitalization and death as endpoints – current indications** In parallel to the above studies, which focused mostly on surrogate functional or echocardiographically-measured endpoints, there was a need for randomized clinical trials testing CRT with heart failure hospitalization or death, and with death alone as the primary endpoints. In the COMPANION trial (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure),[15] 1520 heart failure patients with EF ≤35%, NYHA class III or IV, QRS ≥120 ms were randomized to receive optimal pharmacologic therapy alone or in combination with CRT with either a pacemaker (CRT-P) or a pacemaker-defibrillator (CRT-D). As compared with optimal pharmacologic therapy alone (FIGURE 2), CRT-P decreased the risk of the primary endpoint consisting of death or hospitalization for any cause (hazard ratio 0.81, $P = 0.014$). Similarly, CRT-D significantly decreased the primary endpoint (hazard ratio 0.80, $P = 0.01$). The risk of the combined endpoint of death from or hospitalization for heart failure was reduced by 34% in the CRT-P group ($P < 0.002$) and by 40% in the CRT-D group ($P < 0.001$). There was also a 24% decrease in mortality by CRT-P ($P = 0.059$) and a 36% decrease in mortality by CRT-D ($P = 0.003$).

The CARE-HF study (Cardiac Resynchronization-Heart Failure),[16] enrolled 813 heart failure patients in NYHA class III or IV despite standard pharmacologic therapy, with EF ≤35%, a left LV end-diastolic dimension of at least 30 mm, and a QRS interval of ≥120 ms.

Patients with a QRS interval of 120 to 149 ms were required to meet 2 of 3 additional criteria for dyssynchrony: an aortic pre-ejection delay >140 ms, an interventricular mechanical delay >40 ms, or delayed activation of the posterolateral LV wall. Patients were randomized to conventional medical therapy or CRT-P (without defibrillator). The primary endpoint was a composite of death from any cause or an unplanned hospitalization for a major cardiovascular event. The use of CRT-P therapy was associated with a significant 37% reduction (FIGURE 3) in the primary endpoint (hazard ratio 0.63, $P < 0.001$) and 36% reduction in mortality (hazard ratio 0.64, $P < 0.002$). The CARE-HF trial demonstrated that CRT even without concomitant ICD reduced heart failure hospitalization and mortality.

These 2 landmark studies, COMPANION and CARE-HF, established the clinical indications for CRT, which are currently approved by

the European Society of Cardiology,[17] American College of Cardiology, American Heart Association, and the Heart Rhythm Society.[18] TABLE 1 shows the 2007 European recommendations[17] and TABLE 2 shows the 2008 American recommendations,[18] which are virtually the same with the exception that in the latter there is no additional requirement for the evidence for LV dilation on top of low EF.

**Cardiac resynchronization therapy in less advanced heart failure** Although current indications for CRT require QRS ≥120 ms, there are patients with narrow QRS complexes, who have echocardiographic evidence of LV mechanical dyssynchrony and may benefit from CRT. The ReThinQ[19] trial (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) enrolled 172 heart failure patients with NYHA class III and QRS <130 ms and evidence of mechanical dyssynchrony on echocardiography. Around ¼ of the patients had QRS of at least 120 ms. The primary endpoint was an increase in peak oxygen consumption during cardiopulmonary exercise testing at 6-month follow-up. At 6 months, the CRT group and the control group did not differ significantly in the proportion of patients with the primary endpoint (46% and 41%, respectively). In a prespecified subgroup with a QRS interval ≥120 ms, the peak oxygen consumption increased in the CRT group ($P$ = 0.02), but it was unchanged in a subgroup with a QRS interval of less than 120 ms ($P$ = 0.45). The authors concluded that CRT did not improve peak oxygen consumption indicating that patients with heart failure and narrow QRS intervals may not benefit from CRT. This was a small study, with only 126 patients having QRS <120 ms, therefore, it is premature to definitely claim that CRT will not benefit some patients with dyssynchrony and narrow QRS. Future larger clinical trials will determine whether echocardiography-diagnosed dyssynchrony in patients with QRS <120 ms might identify heart failure patients benefiting from CRT.

In the REVERSE trial (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction),[20] the authors evaluated the effects of CRT in 610 NYHA class II patients and class I patients with previous heart failure symptoms with QRS ≥120 ms and EF ≤40%. The primary endpoint was the heart failure clinical composite response, which scores patients as improved, unchanged, or worsened. The heart failure clinical composite response endpoint, which compared only the percent worsened, indicated that 16% worsened in the CRT-ON group compared with 21% in the CRT-OFF group ($P$ = 0.10). Patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index (–18.4 ±29.5 ml/m$^2$ vs. –1.3 ±23.4 ml/m$^2$, $P$ <0.0001). The time-to-first heart failure hospitalization during a 12-month follow-up was significantly delayed in the CRT-ON group (hazard ratio 0.47; $P$ = 0.03). The REVERSE European investigators[21] extended the follow-up to 24 months in 262 patients from European enrollment and they found that the primary endpoint of worsening reached significance with 19% worsened in the group of CRT-ON vs. 34% in the group with CRT-OFF. Time to first heart failure hospital stay or death in this subset of patients was significantly delayed by CRT (hazard ratio 0.38, $P$ = 0.003). These secondary analyses of the data from the original REVERSE trial provided important preliminary data regarding the beneficial effect of CRT in patients with predominantly NYHA class II heart failure.

The MADIT-CRT trial should be considered as the definitive study regarding the clinical benefit of CRT evaluated in 1820 mild-to-moderate heart failure patients with ischemic (NYHA class I or II) and nonischemic (class II) cardiomyopathy with EF ≤30% and QRS ≥130 ms.[22] The primary endpoint was death from any cause or a nonfatal heart-failure event (whichever came first). During an average 2.4-year follow-up, the primary endpoint occurred in 187 of 1089 patients in the CRT-ICD group (17.2%) and 185 of 731 patients in the ICD-only group (25.3%) (hazard ratio in the CRT-ICD group: 0.66; $P$ = 0.001). There was a 41% reduction in the risk of heart-failure events. FIGURE 4 shows a very significant difference

**TABLE 1** European recommendations for the use of cardiac resynchronization therapy by biventricular pacemaker (CRT-P) or biventricular pacemaker combined with an implantable cardioverter defibrillator (CRT-D) in heart failure patients (2007)[17]

| |
|---|
| **Class I** |
| heart failure patients: |
| who remain symptomatic in NYHA classes III–IV despite OPT |
| with LVEF ≤35% |
| LV dilatation (LV dilatation/different criteria have been used to define LV dilatation in controlled studies on CRT: LV end-diastolic diameter >55 mm; LV end-diastolic diameter >30 mm/m$^2$, LV end-diastolic diameter >30 mm/m [height]), |
| normal sinus rhythm |
| wide QRS complex (≥120 ms) |
| level of evidence: A for CRT-P to reduce morbidity and mortality |
| level of evidence: B, CRT-D is an acceptable option for patients who have expectancy of survival with a good functional status for more than 1 year |
| heart failure patients: |
| with Class I indication for an ICD (first implant or upgrading at device change) who are symptomatic in NYHA classes III–IV despite OPT |
| LVEF ≤35% |
| LV dilatation |
| QRS ≥120 msec |
| level of evidence: B |
| **Class IIa** |
| heart failure patients: |
| who remain symptomatic in NYHA classes III–IV despite OPT |
| with low LVEF ≤35% |
| LV dilatation |
| permanent AF and indication for atrioventricular junction ablation |
| level of evidence: C |

Abbreviations: AF – atrial fibrillation, NYHA – New York Heart Association, OPT – optimal pharmacological therapy, others – see FIGURE 1

**TABLE 2** Recommendations for cardiac resynchronization therapy in patients with severe systolic heart failure (United States, 2008)[18]

| |
|---|
| **Class I** |
| for patients who have: |
| LVEF ≤35% |
| QRS ≥120 ms |
| sinus rhythm |
| CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy. |
| level of evidence: A |
| **Class IIa** |
| for patients who have: |
| LVEF ≤35% |
| QRS ≥120 ms |
| AF |
| CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy. |
| level of evidence: B |
| for patients with: |
| LVEF ≤35% |
| NYHA Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable. |
| level of evidence: C |
| **Class IIb** |
| for patients with: |
| LVEF ≤35% |
| NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered. |
| level of evidence: C |
| **Class III** |
| CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing. |
| level of evidence: B |
| CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions. |
| level of evidence: C |

Abbreviations: see FIGURE 1 and TABLE 1

in the probability of survival free of heart failure in CRT-D vs. ICD in the MADIT-CRT trial achieved on top of optimal medical therapy. There was no significant difference between the 2 groups in the overall risk of death, with a 3% annual mortality rate in each treatment group. CRT was associated with a significant reduction in LV volumes and improvement in the EF (FIGURE 5). Patients with wide QRS duration (prespecified as ≥150 ms) and women derived significantly more benefit from CRT-D than patients with QRS <150 ms and men. These observations are consistent with prior CRT studies indicating that patients with wider QRS complex and more advanced conduction disturbances, namely left bundle branch block, derive more benefit.[11-16] Women have a shorter QRS than men, therefore, the inclusion criterion of at least 130 ms favored enrolling women with more advanced electrical abnormalities. The MADIT-CRT trial provided evidence that CRT very dramatically reduces the progression of heart failure in relatively asymptomatic or mildly symptomatic patients with a low EF and wide QRS complex.

The above 2 studies, especially MADIT-CRT, provide strong evidence and encouragement toward broadening indications for CRT-D therapy. The REVERSE trial included patients with EF ≤40%, whereas the MADIT-CRT focused on patients with EF ≤30%, and most likely the latter group will receive approval for new indications. The question could be asked whether all NYHA class I or II with EF ≤30% should be implanted with CRT-D or whether this therapy should be considered first in patients with wider QRS complex (≥150 ms) or left bundle branch block. There are data indicating that patients with right bundle branch block might not benefit as much as patients with left bundle branch block from CRT.[23-25] Further analyses of the data from MADIT-CRT as well as data from another not yet completed study, RAFT (Resynchronization/Defibrillation in Advance Heart Failure Trial), will substantiate justification for new indications in patients with less advanced heart failure.

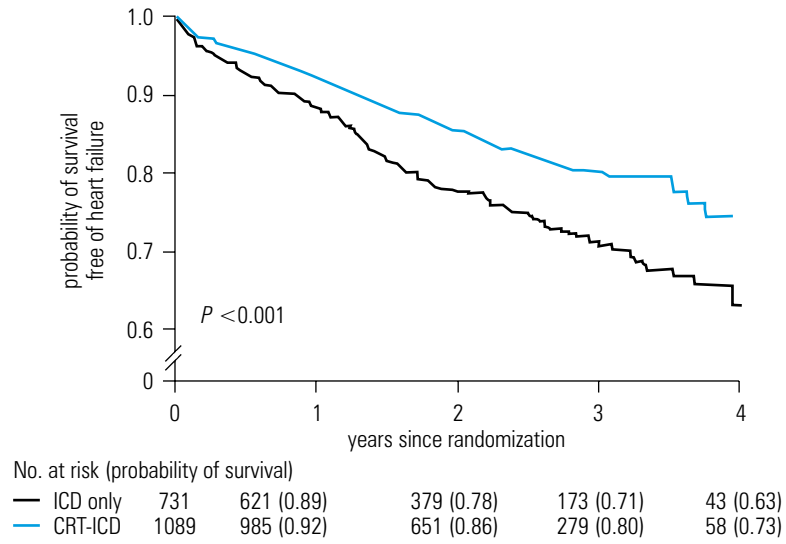


**FIGURE 4** Kaplan-Meier estimates of the probability of survival free of heart failure in CRT-D vs. ICD in the MADIT-CRT.[22] (Copyright © 2010 Massachusetts Medical Society. All rights reserved).

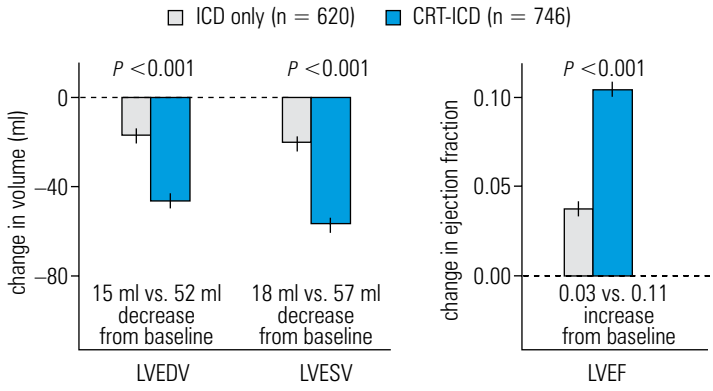


**FIGURE 5** Changes in mean echocardiographic left ventricular volumes and ejection fraction between baseline and 1-year follow-up in CRT-D vs. ICD patients from the MADIT-CRT.[22] (Copyright © 2010 Massachusetts Medical Society. All rights reserved). Abbreviations: LVEDV – left ventricular end-diastolic volume, LVESV – left ventricular end-systolic volume, others – see **TABLES** 1 and 2

**Summary** There is profound clinical evidence from randomized clinical trials that CRT is beneficial in heart failure patients and contributes to a significant decrease in heart failure progression. These beneficial clinical and hemodynamic effects are obtained on top of administering optimal pharmacological therapy and also in the presence of simultaneous protection by ICDs. Currently approved indications for CRT include utilizing this treatment modality in heart failure patients with EF ≤35%, who are eligible for ICD therapy; therefore the CRT-D device is a natural choice for resynchronization therapy. To date, NYHA class III or IV with QRS ≥120 ms has been required in such patients, but new data from clinical trials (MADIT-CRT in particular) indicate that a more proactive approach should be considered and patients with less advanced heart failure might also be suitable candidates for CRT-D therapy.

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ARTYKUŁ POGLĄDOWY

# Których chorych z przewlekłą niewydolnością serca należy kierować do wszczepienia urządzenia resynchronizującego i defibrylującego (CRT-D)?

## Praktyczne implikacje najnowszych badań klinicznych

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**SŁOWA KLUCZOWE**

kardiomiopatia, kardiowerter defibrylator, leczenie resynchronizujące, niewydolność serca

**STRESZCZENIE**

W ostatnim dziesięcioleciu leczenie resynchronizujące (*cardiac resynchronization therapy* – CRT) stało się ważną metodą leczenia chorych z niewydolnością serca. Prewencja pierwotna zgonu za pomocą wszczepialnego kardiowertera-defibrylatora (*implantable cardioverter-defibrillator* – ICD) u chorych z kardiomiopatią niedokrwienną i inną niż niedokrwienna oraz z dysfunkcją lewej komory (frakcja wyrzutowa ≤35%) stała się standardem opieki. Coraz większa liczba chorych ze wskazaniami do ICD kwalifikuje się również do CRT i otrzymuje urządzenia resynchronizująco-defibrylujące (CRT-D). W badaniach z randomizacją dowiedziono, że CRT daje korzyści u chorych z niewydolnością serca, i że stosowana dodatkowo do optymalnej farmakoterapii przyczynia się do znamiennego zmniejszenia progresji niewydolności serca. Do aktualnych wskazań do CRT-D należy wykorzystanie tej metody u chorych z niewydolnością serca w III lub IV klasie NYHA, frakcją wyrzutową ≤35% i QRS ≥120 ms. Nowe dane z badania MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy) wskazują, że chorzy z mniej zaawansowaną niewydolnością serca (kardiomiopatia niedokrwienna w I lub II klasie NYHA i kardiomiopatia inna niż niedokrwienna w klasie II), frakcją wyrzutową ≤30% oraz QRS ≥130 ms mogą również odnieść korzyści z CRT. Sugeruje to, że u chorych z mniej nasiloną niewydolnością serca należy rozważyć bardziej zdecydowane leczenie, aby zmniejszyć progresję niewydolności serca za pomocą CRT-D.

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