# Cardiac Resynchronization Therapy: Long-Term Alternative to Cardiac Transplantation?

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*Background.* **Cardiac transplantation remains the gold standard for treating end-stage heart failure. However, because of donor shortage and posttransplant complications alternative options are needed.**

*Methods.* **We investigated the impact of cardiac resynchronization therapy on clinical outcome in 545 patients with left bundle-branch block and interventricular asynchrony, who fulfilled the cardiac criteria for cardiac transplantation listing. Primary end point was heart failure death. Secondary end points were New York Heart Association class, functional (cardiopulmonary exercise tolerance, 6-minute hall walk distance), and morphologic (left ventricular end-diastolic diameter) factors.**

*Results.* **The average follow-up period was 39.6 months (standard deviation, 26.1 months). In total, 1,784 years of observation were accrued. The percentage of nonresponders (no functional and morphologic improvement during follow-up) was 21.2%. One-year and 3-year freedom from heart failure death was 92.3% and 77.3%, respectively. Functional variables improved, but the left ventricular end-diastolic diameter decreased during the first 6 months of cardiac resynchronization therapy only in patients who survived during follow-up. Under cardiac resynchronization therapy, 42.5% (n = 34) of the cardiac transplantation candidates with atrial fibrillation at baseline returned to sinus rhythm.**

*Conclusions.* **Our data suggest that cardiac resynchronization therapy is a reliable long-term therapeutic option for the treatment of end-stage heart failure and intraventricular asynchrony.**

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Cardiac transplantation (CTx) remains the gold standard for treating end-stage heart failure [1, 2]. However, worldwide donor shortage and posttransplant complications such as cardiac rejections, graft vasculopathy, and drug-induced renal impairment led to the search for alternative therapeutic strategies. The implantation of ventricular assist devices significantly prolongs survival in end-stage heart failure patients [3–5], but ventricular assist device implantation is mostly used as a bridge to transplant. In less severely affected heart failure patients, pharmacologic treatment may reduce mortality. In huge randomized multicenter trials, cardiac resynchronization therapy (CRT) was shown to reduce symptoms and to improve left ventricular (LV) function in patients with congestive heart failure caused by LV dyssynchrony [6, 7]. Consequently, various guidelines list CRT as a therapeutic option in congestive heart failure patients [8, 9]. Cardiac resynchronization therapy has also been discussed as an alternative to CTx in advanced heart failure, although data on this are scarce [10, 11]. Moreover, it is presently not clear whether CRT can prevent CTx in the long run. Therefore, we aimed to assess the long-term clinical outcome in a large cohort of CTx candidates who received CRT systems at our institution during recent years.

## Patients and Methods

### *Patients*

Our report summarizes data obtained at the Heart and Diabetes Center North-Rhine Westfalia, Bad Oeynhausen, Germany, between November 1997 and October 2006. During this period, 729 patients received CRT

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systems. Patients were selected for CRT by the following criteria: pulse pressure increase of 10% or greater during preimplantation testing [11], left bundle-branch block with interventricular asynchrony [12], and an electrocardiographically verified QRS width of 150 milliseconds or greater. The most important criteria for CRT was left bundle-branch block in the electrocardiogram. After publication of the CRT guidelines in 2005 [11–13], we amended our selection criteria and also accepted patients with narrow QRS complexes if tissue Doppler imaging demonstrated LV dyssynchrony. None of the patients considered for CRT needed cardiac surgery for coronary stenosis, aortic valve defects, or mitral valve stenosis. A total of 545 CRT patients (74.8% of the 729 patients) with a mean age at implant of 62.5 years (range, 2 to 83 years) fulfilled at least three of the following four criteria for cardiac transplantation of the German Medical Association at baseline: New York Heart Association (NYHA) functional class IV, LV ejection fraction (LVEF) less than 0.20, LV end-diastolic diameter (LVEDD) greater than 75 mm, and maximal oxygen consumption ($\dot{V}O_2max$) not greater than 10 to 14 $mL \cdot kg^{-1} \cdot min^{-1}$. These 545 patients were included in the data analysis. Contraindications to cardiac transplantation (comorbidities) such as malignancies were not considered. Among the total number of 545 patients, 395 had a QRS duration of 150 milliseconds or greater (range, 150 to 320 milliseconds) and 150 had a QRS duration of less than 150 milliseconds (range, 100 to 149 milliseconds). Initially, almost all patients received biventricular pacemakers (CRT-P) without defibrillator function (n = 94). After CRT systems with defibrillator function (CRT-D) became available in July 1999, a rapidly increasing number of patients received CRT-D devices (n = 451). Owing to ventricular episodes, the CRT-P system had to be upgraded to a CRT-D system in 24 patients. In 2 patients, infected systems mandated explantation and contralateral reimplantation of a new CRT-D system. The Ruhr University Ethics Committee, Bochum, Germany, approved the study, and the need for individual informed consent was waived.

### *Study Procedures*

We considered heart failure death during CRT as the primary end point. Secondary end points were NYHA classification, functional (cardiopulmonary exercise tolerance, 6-minute hall-walk distance [HWD]), and morphologic variables (LVEDD). These factors allow us to differentiate among subjective outcome (NYHA classification), functional outcome (exercise tolerance and HWD), and morphologic outcome (LVEDD).

In addition to individual characteristics (age, sex, diagnosis, LVEF, cardiac rhythm, comorbidities), all variables were assessed at baseline and for up to 84 months during regular follow-up visits (1 and 3 months after device implantation followed by quarterly visits). We measured $\dot{V}O_2max$ by cardiopulmonary exercise testing, maximal workload by ergometry, 6-minute HWD by counting meters, and LVEDD by echocardiography. The cardiac rhythm (sinus rhythm, intermittent or permanent atrial fibrillation [AFib]) was assessed by electrocardiographic analysis during follow-up visits and by recalling information regarding mode switch episodes from the CRT system's Holter monitor.

Efficacy of CRT was determined by assessing improvements in morphologic outcome at the last follow-up in comparison to baseline values. For this purpose, patients were divided into subgroups of morphologic responders (LVEDD reduction greater than 10%), nonprogressors (LVEDD reduction 0% to 10% but functional improvement), and nonresponders (LVEDD values greater than baseline value or functional deterioration). Moreover, above baseline $\dot{V}O_2max$ values, workload, or 6-minute HWD results during follow-up were indicative of functional improvement. For data analysis, we also assessed outcome variables in patients cataloged by diagnosis (dilated cardiomyopathy [DCM], coronary heart disease [CHD]) and cardiac rhythm (sinus rhythm or atrial fibrillation). In patients with DCM, we also looked for age-specific differences in outcome variables (age $\leq$ 60 years and age $>$ 60 years).

### *Statistics*

Categorical variables are reported using the number (N) and percent of observations. Continuous variables are expressed as mean values with standard deviation. We tested normal distribution of the data using the Kolmogorov-Smirnov test. Normal distribution was considered if probability values were greater than 0.05. Data were then evaluated using the $\chi^2$ test and the unpaired Student's *t* test when appropriate. Event rates were calculated using the Kaplan–Meier product-limit estimator. Those patients who received ventricular assist device implantation or were listed with Eurotransplant for CTx were censored. Analysis of variance and two-factor repeated-measures analysis of variance with time and subgroup of patients were used to analyze outcome variables when appropriate. Post hoc analyses were based on the Tukey test and the Student's *t* test when appropriate. We used the statistical software package SPSS, version 14 (SPSS Inc, Chicago, IL), to perform the analyses.

## Results

Baseline characteristics such as sex distribution, age, diagnosis, comorbidities, and cardiac variables of the study cohort are presented in Table 1. Mean LVEF values were 0.181 ± 0.034. All patients with LVEF values greater than 0.20 ± 0.108 showed cardiac decompensation and fulfilled the other three criteria for CTx listing. Mean baseline values of $\dot{V}O_2max$, workload, 6-minute HWD, and LVEDD were 11.3 ± 2.9 $mL \cdot kg^{-1} \cdot min^{-1}$, 50.1 ± 22.0 W, 265 ± 112 m, and 78.2 ± 10.2 mm, respectively.

The average follow-up period was 39.6 ± 26.1 months. The 545 patients accrued 1,784 years of observation. The probability of survival during CRT is given in Figure 1. One-year, 2-year, and 3-year survival was 92.3%, 85.0%, and 77.3%, respectively. One hundred twenty-eight patients died during CRT, 12 patients had ventricular assist device implantation, 42 patients underwent transplantation, and 6 patients are still listed with Eurotransplant for CTx. In total, 111 patients were listed at Eurotransplant (50 patients before CRT and 61 after CRT). Thirty-five patients could be unlisted later on as a result of long-term improvement (20 before CRT, 15 after CRT). Of the 128 CTx candidates who died, 28 patients were on the waiting list. The other 100 patients had relative or absolute contraindications for CTx listing with Eurotransplant (94 patients were older than 65 years, 11 patients had malignancies). Twenty-four CTx candidates died within the first 6 months of CRT implantation.

In total, 37.2% of the study cohort were morphologic responders, 41.6% nonprogressors, and 21.2% nonresponders.

In Figure 2, subjective, functional, and morphologic outcome variables are presented for the first 6 months of CRT in 492 of the 545 CTx candidates according to the primary end point of cardiac death. Of the remaining 53 CTx candidates whose data are not presented, 24 patients died within the first 6 months of CRT and 29 patients had at least one missing data point. Data in Figure 2 demonstrate that the NYHA class decreased during follow-up, and functional factors improved in both groups, but LVEDD improved only in the event free group.

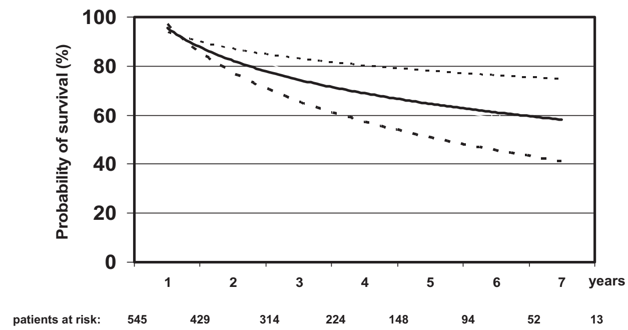


*Fig 1. Kaplan–Meier estimates of freedom from therapy failure in cardiac transplant candidates with cardiac resynchronization therapy. Dotted lines indicate 95% confidence intervals.*

*Table 1. Characteristics and Outcome Variables of the Study Cohort at Baseline*

| Variable | Number (N = 545) | Percentage |
|---|---|---|
| Males (%) | 426 | 78.2 |
| Age category (y) | | |
| <20 | 3 | 0.6 |
| 20–44 | 38 | 7.0 |
| 45–69 | 468 | 85.9 |
| ≥70 | 36 | 6.6. |
| Diagnosis (%) | | |
| Dilated cardiomyopathy | 273 | 50.1 |
| Coronary heart disease | 225 | 41.3 |
| Others | 47 | 8.6 |
| Concomitant diagnosis (%) | | |
| COPD | 56 | 10.3 |
| Renal insufficiency[a] | 132 | 24.2 |
| Pulmonary hypertension | 161 | 29.6 |
| Diabetes mellitus | 162 | 29.7 |
| Malignancy | 42 | 7.7 |
| Central neurologic defect | 46 | 8.4 |
| Obesity | 85 | 15.6 |
| Atrial fibrillation (%) | 80 | 14.7 |
| Defibrillator implantation (%) | 472 | 86.6 |
| NYHA class III or IV (%) | 488 | 89.55 |
| $\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$) | | |
| <10 | 131 | 24.0 |
| 10–14 | 260 | 47.7 |
| >14 | 391 | 28.2 |
| Left ventricular ejection fraction | | |
| ≤0.20 | 486 | 89.2 |
| >0.20–0.30 | 59 | 10.8 |
| LVEDD (mm) | | |
| <75 | 182 | 33.4 |
| >75 | 363 | 66.6 |

[a] Serum creatinine > 1.6 mg/dL.

COPD = chronic obstructive pulmonary disease; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association; $\dot{V}O_2max$ = maximal oxygen consumption.

In Table 2, outcome variables are shown by diagnosis up to 60 months. New York Heart Association functional class and functional variables ($\dot{V}O_2max$ and 6-minute HWD) improved in both DCM and CHD patients to a similar extent during follow-up. However, LVEDD improved in more patients with DCM, but not as much in patients with CHD. Among patients in the DCM subgroup, 42.9% were morphologic responders, 38.5% were nonprogressors, and 18.7% were nonresponders. The corresponding values for the CHD subgroup were 30.2% responders, 45.3% nonprogressors, and 24.4% nonresponders—a result significantly different from the DCM group ($p = 0.013$). Survival did not differ significantly between subgroups (data not shown).

In the DCM subgroup, we also investigated the effect of age at implant (age ≤ 60 years and age > 60 years) on functional and morphologic outcome. However, results did not differ between age classes (data not shown).

At baseline, 80 of the 545 patients were in atrial fibrillation (AFib); 13 patients with permanent AFib had already received a VVI pacemaker and 3 patients a DDD pacemaker. Intermittent AFib at baseline was observed in 18 of the remaining 465 patients who were in sinus rhythm. In 44 additional patients, a DDD pacemaker had already been implanted because of high-degree atrioventricular (AV) blocks.

Twenty-four CTx candidates (5.2%) who were initially in sinus rhythm exhibited persistent AFib during follow-up. Thirty-four patients (42.5%) of the 80 patients with initially permanent AFib regained sinus rhythm during CRT.

## Comment

Because of the worldwide donor shortage and posttransplant complications in CTx recipients, new therapeutic

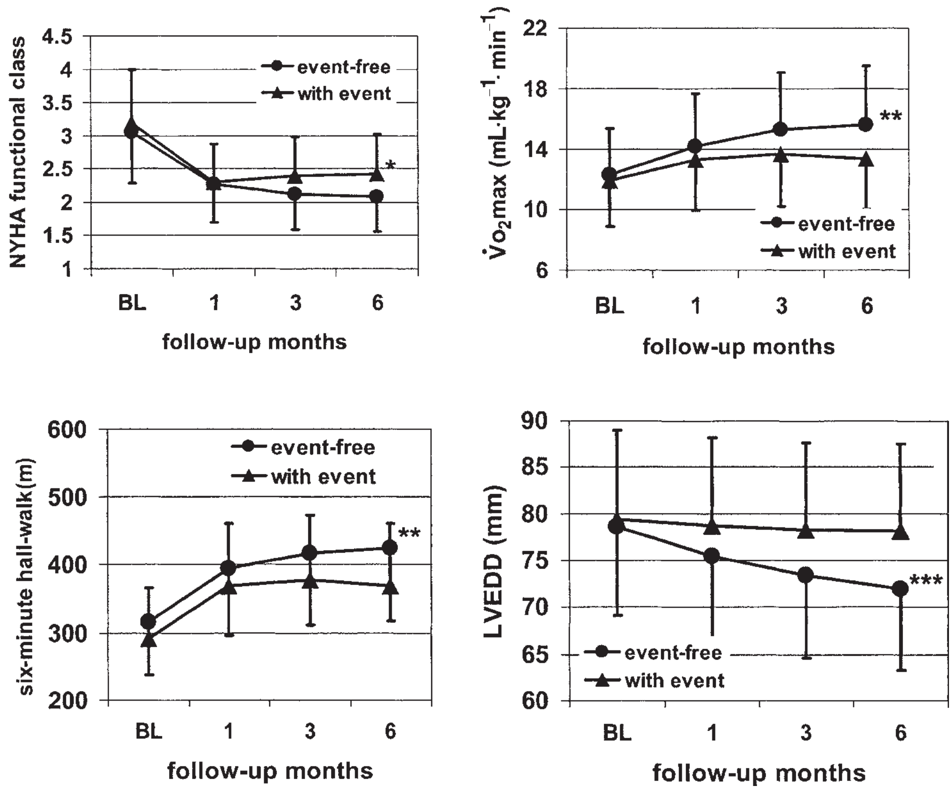


*Fig 2. Time course of various outcome variables during the first 6 months of cardiac resynchronization therapy in cardiac transplant candidates who survived (N = 381) or did not survive (N = 111) during follow-up. The two-factor repeated-measures analysis of variance revealed significant time effects for New York Heart Association (NYHA) class ($p < 0.001$), maximal oxygen consumption ($\dot{V}O_2max$; $p < 0.001$), 6-minute hall-walk distance ($p < 0.001$), and left ventricular end-diastolic diameter (LVEDD; $p < 0.001$). Significant differences between groups were present for New York Heart Association class ($p < 0.05$), maximal oxygen consumption ($p < 0.01$), 6-minute hall-walk distance ($p < 0.01$), and left ventricular end-diastolic diameter ($p < 0.001$). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ between patients with and without an event during follow-up. (BL = baseline.)*

options for end-stage heart failure are urgently needed. This study demonstrates in a large study cohort that CRT is a viable option with an acceptable mid-term and long-term outcome in CTx candidates with LV dyssynchrony. The 1-year and 3-year freedom from heart failure death in our CTx candidates (92.3% and 77.3%, respectively) must be regarded in light of the reported 1-year mortality rates of up to 50% and more in pharmacologically treated end-stage congestive heart failure patients with NYHA functional class III or IV and a median EF value of 0.18 [14]. Our data confirm results of an earlier small study in congestive heart failure patients [15]. In that earlier investigation, cumulative survival after a follow-up of 488 ± 346 days was 92% in patients with CRT compared with 39% in patients without CRT. Similar to our CTx candidates at baseline, mean NYHA functional class was 3.1 ± 1.1, and the mean LVEF value was 0.20 ± 0.11 in the patients of that earlier study. Even in reports describing mortality rates in CTx recipients, including reports from our own heart center, the 1-year and 3-year survival rates of 81% to 88% and 74% to 82%, respectively [16, 17], are not higher than those in our CTx candidates with CRT. It is noteworthy that the vast majority of CTx candidates who died during CRT were 65 years and older. Their chance of CTx would have been very limited.

Cardiac function improves continuously during CRT (Fig 2). This is essential for the long-term survival of patients with reduced LVEF and QRS complex longer than 120 milliseconds [6, 18]. Even after eliminating errors such as incorrect patient selection, inaccurate LV lead placement, and suboptimal device programming [19], up to 30% of patients are reported to be nonresponders in the long run [20, 21]. The percentage of nonresponders in our CTx candidates (21.2% of 545 patients) was similar to the percentage of nonresponders in the aforementioned earlier studies. Notably, the percentage of nonresponders in our patients was similar to the total number of 128 patients who died.

Despite a slight transient improvement in functional variables within the first 3 months, it was obvious that in our patients who experienced an event later on, CRT did not result in an improved LVEDD within the first 6 months. Unless CTx is contraindicated, these patients should be rapidly listed for CTx if no concomitant improvement in functional variables occurs. In Figure 3, we present the allocation scheme used at our institution. In case of significant functional or morphologic improvement on the waiting list, patients are first temporarily listed 'not transplantable' and are then unlisted later on (15 of 61 after CRT listed patients). This avoids an unacceptable increase in the individual waiting time for CTx. Without long-term improvement in cardiac function, CRT can still be used as a bridge to transplant [22, 23].

The development of AFib during follow-up is a complication that is probably related to poor ventricular function resulting in atrial enlargement and secondary mitral regurgitation. As a consequence, total cardiac capacity will be reduced. These patients will only reach their preexisting cardiac capacity if a stable sinus rhythm is restored. Therefore, it seems reasonable to handle newly occurring AFib by medication and aggressive interventional treatment such as AFib ablation or AV

*Table 2. Time Course of Various Outcome Variables in Cardiac Transplantation Candidates With Dilated Cardiomyopathy and Coronary Heart Disease*

| Variable | Baseline | After 3 mo | After 6 mo | After 12 mo | After 24 mo | After 36 mo | After 48 mo | After 60 mo | *p* Value for Change Within Groups | *p* Value for Difference versus CHD | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | At BL | At 60 mo |
| DCM (n) | 273 | 258 | 252 | 223 | 158 | 105 | 70 | 49 | | | |
| CHD (n) | 225 | 215 | 219 | 187 | 131 | 87 | 59 | 40 | | | |
| NYHA class | | | | | | | | | | | |
| DCM | 3.05 ± 1.05 | 2.15 ± 1.00 | 2.08 ± 0.89 | 2.03 ± 0.96 | 2.09 ± 0.96 | 2.03 ± 0.95 | 2.05 ± 0.92 | 1.98 ± 0.98 | <0.001 | 0.078 | 0.198 |
| CHD | 3.11 ± 1.10 | 2.29 ± 1.06 | 2.31 ± 0.87 | 2.25 ± 1.00 | 2.28 ± 0.94 | 2.21 ± 0.87 | 2.3 ± 0.97 | 2.27 ± 1.01 | <0.001 | | |
| $\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$) | | | | | | | | | | | |
| DCM | 12.4 ± 3.9 | 15.6 ± 3.1 | 15.6 ± 3.9 | 16.1 ± 3.1 | 16.5 ± 3.5 | 17.1 ± 3.8 | 16.7 ± 2.7 | 17.2 ± 3.4 | <0.001 | 0.017 | 0.092 |
| CHD | 11.7 ± 2.8 | 13.7 ± 3.6 | 13.9 ± 2.7 | 14.6 ± 3.7 | 14.3 ± 3.3 | 14.7 ± 3.0 | 15.2 ± 2.9 | 15.4 ± 3.0 | <0.001 | | |
| HWD (m) | | | | | | | | | | | |
| DCM | 319 ± 112 | 420 ± 113 | 418 ± 120 | 429 ± 129 | 431 ± 135 | 434 ± 145 | 433 ± 126 | 428 ± 136 | <0.001 | 0.06 | 0.205 |
| CHD | 290 ± 128 | 382 ± 118 | 388 ± 109 | 403 ± 140 | 395 ± 127 | 404 ± 127 | 417 ± 127 | 399 ± 128 | <0.001 | | |
| LVEDD (mm) | | | | | | | | | | | |
| DCM | 82.3 ± 13.1 | 77.0 ± 12.7 | 75.3 ± 10.8 | 73.9 ± 13.5 | 69.8 ± 13.1 | 66.9 ± 12.1 | 66.5 ± 11.1 | 65.1 ± 13.7 | <0.001 | <0.001 | <0.01 |
| CHD | 75.7 ± 12.8 | 73.4 ± 14.1 | 72.8 ± 12.9 | 71.8 ± 12.8 | 71.1 ± 14.7 | 70.6 ± 10.9 | 72.2 ± 12.4 | 72.3 ± 13.9 | 0.089 | | |

BL = baseline; CHD = coronary heart disease; DCM = dilated cardiomyopathy; HWD = 6-min hall-walk distance; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association; $\dot{V}O_2max$ = maximal oxygen consumption.

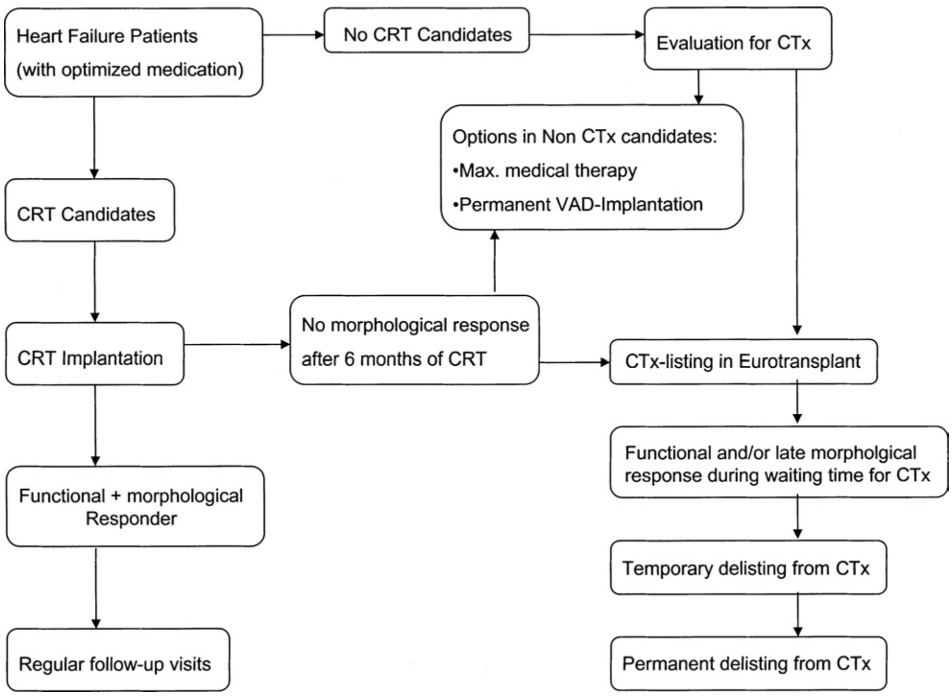


*Fig 3. Allocation scheme for cardiac resynchronization therapy (CRT) or cardiac transplantation (CTx). (VAD = ventricular assist device.)*

node ablation. However, our data also show that a significant percentage of patients with AFib regained sinus rhythm during CRT. In line with earlier recommendations [24], these results demonstrate that a high percentage of patients with persistent AFib could benefit from CRT. Although AV node ablation is preferred by some authors [25], we believe that this procedure is only necessary if the rhythm cannot be controlled by other means. Without AV node ablation, the native AV conduction can be used and unphysiologic right ventricular stimulation may be avoided. Therefore, AV node ablation should be performed only as a last option resort.

In line with some [26, 27] but not all [28] earlier results, we could demonstrate that the percentage of morphologic responders was significantly higher in the subgroup of patients with DCM than in the subgroup of CHD patients. Especially in CHD patients, reversed remodeling of the left ventricle is often impossible because of preexisting myocardial scars [29, 30]. However, even in the long run, functional variables improved to a similar extent, and clinical outcome was comparable between DCM and CHD patients. Consequently, CTx candidates obviously can benefit from CRT, even if no reversed remodeling in CHD patients occurs. This is an important finding, as CHD patients differ from those patients who experience an event. In contrast to the subgroup of CHD patients, the subgroup of patients with an event shows no improvement in morphologic and functional variables. The fact that there is no generally accepted definition of response to CRT remains an issue. Several preoperative variables such as age, sex, and diagnosis as well as initial hemodynamic improvement and various laboratory variables were not able to predict the long-term benefit of CRT [31]. We suggest considering only those patients as nonresponders who (1) do not show functional improvement after 2 years of CRT, (2) show LV enlargement, (3) have to be transplanted, or (4) die of heart failure.

Our results confirm earlier data that the success of CRT was independent of age in the subgroup of DCM patients [32, 33].

Our study has some limitations. First, no data on LVEF were available during follow-up. However, LVEDD is a reliable variable for assessing morphologic outcome. Second, we changed our treatment strategy from CRT-P devices to CRT-D devices during follow-up. Because of a reduction in the rate of sudden death, CRT-D devices significantly improve long-term survival compared with CRT-P devices [34, 35]. In the present study, we could minimize the risk of sudden death by early implantation of a CRT-D device in those patients who showed episodes of ventricular fibrillation during follow-up using the system's Holter monitor. Thus, the CRT-P system was exchanged for a CRT-D system in 24 patients, whereas only 3 patients with a CRT-P device died suddenly during follow-up. Thus, outcome was not significantly influenced by the type of CRT system. Third, some may argue that the CTx candidates may have done as well without CRT. However, owing to the severity of the disease and in accordance with the CRT guidelines in 2005 it would have been unethical to test this hypothesis by using a control group without CRT. Note that by definition all CTx candidates had end-stage heart failure despite maximal pharmacologic therapy.

In summary, we could demonstrate that CRT is a reliable therapeutic option for the long-term treatment of end-stage heart failure and LV dyssynchrony. Only those CTx candidates who showed no improvement in functional and morphologic outcome within 6 months of CRT should be considered for CTx. This strategy should result in a significant relief of an institution's transplant program.

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