International Journal of Cardiology 263 (2018) 48–53

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiac resynchronization therapy in the ageing population – With or without an implantable defibrillator?

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ARTICLE INFO

Article history:
Received 8 November 2017
Received in revised form 9 March 2018
Accepted 19 March 2018

Keywords:
Heart failure
Cardiac resynchronization therapy
Implantable cardioverter defibrillator
Sudden cardiac death
All-cause mortality

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an effective treatment option for systolic heart failure, but the benefit of an additional implantable cardioverter-defibrillator (ICD) in elderly patients is not well established. The aim of our study was to evaluate the impact of an additional ICD on survival in elderly CRT recipients.

Methods: Patients aged ≥75 years with an indication for CRT and primary preventive ICD therapy, which underwent implantation of either a CRT-pacemaker (CRT-P) or CRT-defibrillator (CRT-D) were included in the study. Patient characteristics, procedural and follow-up data, and subsequent all-cause mortality were analyzed.

Results: A total of 775 consecutive patients underwent CRT implantation, whereof 177 patients fulfilled the inclusion criteria. Of these, 80 patients with CRT-P and 97 with CRT-D formed the two study groups. Patients in the CRT-P group were significantly older (82.6 ± 4.5 vs. 77.8 ± 1.9 years, $p < 0.001$) and more often female (44 vs. 25%; $p < 0.001$), had a better left ventricular ejection fraction (29.5 ± 5.7 vs. 27.4 ± 6.0%; $p = 0.019$) and narrower QRS-complex (150 ± 19 vs. 158 ± 18 ms; $p = 0.025$). During a mean follow-up of 26 ± 19 months, 62 (35%) study patients died, 28 (35%) in the CRT-P and 34 (35%) in the CRT-D group ($p = 0.994$). The Kaplan-Meier analysis of survival probability showed no significant difference between the two groups ($p = 0.562$).

Conclusion: In our study, an additional ICD had no impact on survival in elderly patients undergoing implantation of a CRT device. Randomized controlled trials have to confirm this finding.

1. Introduction

Cardiac resynchronization therapy (CRT) is an established treatment option for systolic heart failure (HF) and proved to be effective even in elderly patients by improving heart failure symptoms and quality of life [1]. The implantation of an implantable cardioverter defibrillator (ICD) has shown to reduce sudden cardiac death (SCD) and all-cause mortality in the same patient cohort with HF and poor left-ventricular ejection fraction (LVEF) [2,3]. As a consequence, it is generally believed that adding a defibrillator to CRT (CRT-D) would further reduce mortality as compared to CRT alone (CRT-P). Therefore, the majority of CRT recipients in Europe and the United States are implanted with a CRT-D device [4].

However, candidates for CRT in clinical practice are often older than those included in the large primary prevention ICD trials and have more often relevant comorbidities, which have been shown to be a significant predictor of mortality in CRT-D recipients [5]. While different studies demonstrated a survival benefit in patients treated with CRT, [6] the only randomized controlled trial comparing CRT-P with CRT-D was not designed to detect a difference in survival between patients treated with either device type [7]. In addition, results obtained from study populations with a mean age of <70 years certainly cannot be transferred to an elderly population with many CRT recipients aged 75 years and older.

The guidelines for ICD implantation demand a patient's life expectancy of >1 year with good functional status, but estimating life expectancy may be complex and the decision to abstain from ICD therapy can be difficult. A simple clinical risk score model including 1) age above 70 years, 2) renal insufficiency (defined as blood urea nitrogen >26 mg/dl), 3) atrial fibrillation, 4) NYHA functional class >II, and 5) a QRS complex >120 ms on surface ECG, is able to predict clinical benefit of primary preventive ICD therapy in patients with ischemic cardiomyopathy [8,9]. Patients with 3 or more of these risk factors were shown to have no mortality benefit from ICD therapy due to the high competing

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[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2018.03.087
0167-5273/

risk of non-arrhythmic death. Since the majority of elderly patients with an indication for CRT have at least 3 risk factors (i.e. age, NYHA functional class, and QRS-duration), the additional benefit of an ICD in this population remains questionable.

Furthermore, implantation of a CRT-D is associated with higher risk of procedure- and device-related complications [10,11] including inappropriate ICD interventions, and higher costs for the health care system [12]. Therefore, the aim of our study was to evaluate the effect of an additional ICD on all-cause mortality in elderly patients undergoing CRT implantation.

2. Methods

2.1. Study population

All consecutive patients aged ≥75 years, who underwent de novo implantation of either a CRT-P or CRT-D device in the department of electrophysiology in the Heart Center Leipzig between January 2008 and August 2014, were screened. Patients were divided into two groups according to the implanted device. Only patients with an established indication for CRT [13] and primary preventive ICD therapy [14,15] were included in the study. Therefore, patients implanted with a CRT-P for antibradycardia pacing in the presence of mildly to moderately impaired LVEF and those implanted with a CRT-D for secondary prevention of SCD were excluded from further analysis.

2.2. Implantation

The decision whether to implant a CRT-P or CRT-D was taken at the discretion of the treating cardiologist in consideration of the medical history, relevant comorbidities, and patient preference. The implantation procedure was performed under local anesthesia with transvenous placement of a right atrial (RA) lead in the RA appendage, a right ventricular (RV) lead in the RV apex, mid-septal RV or septal RV outflow tract, and a left ventricular (LV) lead in a suitable side branch of the coronary sinus, preferably at a non-apical lateral or posterior position. All implanted devices were programmed to DDD-mode (60–140 bpm) with short AV-intervals to achieve a maximum of biventricular stimulation. A conservative programming with a VT-zone at 170–180 bpm, a VF-zone at 210–220 bpm and short intervals for detection of ventricular arrhythmias was utilized in patients implanted with CRT-D. Patient characteristics, periprocedural and follow-up data and complications were recorded and compared between the two study groups.

2.3. Follow-up

Patients were initially followed at 1 month after implantation and subsequently at regular 4- to 6-month intervals for clinical evaluation, device interrogation, and recording of device-related complications. Follow-up diagnostics and treatment were adjusted to the patient's clinical needs at the discretion of the treating cardiologist. For patients who had no follow up in the outpatient clinic, data of their vital status, device-related complications, and appropriate or inappropriate ICD interventions were obtained from the referring cardiologists, relatives, or legal authorities. Follow-up data and all-cause mortality were compared between the two groups. The study was approved by the institutional ethical review board and all subjects gave written informed consent.

2.4. Data analysis

All data were tested for normal (Gaussian) distribution using the Kolmogoroff-Smirnov test.

Continuous variables were expressed as means and ± standard deviation (SD). Categorical variables are presented as number and percentage of patients. Continuous variables were compared by means of Student's *t*-test and categorical variables by Chi-square test. Kaplan–Meier estimates were generated for mean survival. To adjust for 5 clinical relevant covariates (age, sex, LV-EF, type of cardiomyopathy, and number of risk factors) a Cox proportional hazards regression model was used. A two-tailed p value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows, V. 22 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population

Between January 2008 and August 2014, a total of 775 consecutive patients underwent de novo implantation of a CRT device in the department of electrophysiology in the Heart Center Leipzig. Two hundred forty-five patients (32%) were ≥ 75 years of age and screened for inclusion. Out of these, 121 patients (49%) were implanted with a CRT-P and 124 patients (51%) with a CRT-D device. In the CRT-P group, 41 patients had an indication for antibradycardia pacing in the presence of mildly to moderately impaired LV function and were excluded from analysis. In the CRT-D group, 27 patients did not fulfill the inclusion criteria: 23 patients were implanted for secondary prevention of SCD, 3 patients were not implanted with an LV lead, and 1 patient presenting with a narrow QRS complex was included in the ECHO-CRT trial [16]. Thus, the study cohort consisted of 177 elderly patients, 80 (45%) in the CRT-P and 97 (55%) in the CRT-D arm.

3.2. Patient characteristics

Important clinical characteristics of the 2 study groups are presented in Table 1. Patients implanted with a CRT-P were significantly older and more often female, had the better baseline LVEF and narrower QRS complex. Patients implanted with a CRT-D revealed a larger LV end-diastolic diameter and were more often on beta-blockers and aldosterone receptor antagonists. Importantly, 94% of patients overall and in each group presented with 3 or more of the above mentioned risk factors. There were no significant differences in the number and distribution of these risk factors between groups.

One patient, who primarily refused implantation of a defibrillator, presented with a sustained ventricular tachycardia (VT) 10 days after discharge and was upgraded to a CRT-D device. In the CRT-D group, 3 patients were downgraded to CRT-P at the time of first generator replacement at the physician's discretion and patient choice. Another 3 patients in this study group developed a device related infection and had to be explanted. All the above mentioned patients were excluded from further analysis after the intervention.

Table 1
Patient characteristics of the two study groups. Continuous variables are displayed as mean ± standard deviation, categorical variables as number and percentage of the study group.

Patient characteristics	CRT-P group	CRT-D group	p-Value
Number, n	80	97	
Age, y	82.6 ± 4.5	77.8 ± 1.9	<**0.001**
Male, n (%)	45 (56.3)	74 (75.5)	**0.005**
Ischemic dilated cardiomyopathy, n (%)	40 (50.0)	52 (53.1)	0.733
Non-ischemic dilated cardiomyopathy, n (%)	40 (50.0)	46 (46.9)	0.733
Left-ventricular ejection fraction, %	29.6 ± 5.9	27.4 ± 6.0	**0.015**
LVED, mm	57 ± 7	62 ± 8	<**0.001**
NYHA-class, n (%)			0.811
II	13 (16.3)	16 (16.5)	
III	63 (78.7)	78 (80.4)	
IV	4 (5.0)	3 (3.1)	
Atrial fibrillation, n (%)	19 (23.8)	20 (20.4)	0.617
QRS duration, ms	150 ± 19	158 ± 18	**0.025**
Type of block, n (%)			0.157
Left bundle branch block (LBBB)	44 (55.0)	65 (67.0)	
Right bundle branch block (RBBB)	1 (1.3)	2 (2.1)	
Left anterior fascicular block (LAFB)	4 (5.0)	5 (5.2)	
RBBB/LAFB	3 (3.8)	7 (7.2)	
2nd degree AV-block	7 (8.8)	2 (2.1)	
3rd degree AV-block	21 (26.3)	16 (16.5)	
Blood urea nitrogen, mg/dl	30 ± 12	31 ± 14	0.475
Number of risk factors[a], n (%)			0.531
2	5 (6.3)	6 (6.2)	
3	24 (30.0)	34 (35.0)	
4	45 (56.2)	45 (46.4)	
5	6 (7.5)	12 (12.4)	
Cardiac medication, n (%)			
Beta-blocker	64 (80.0)	88 (90.7)	**0.042**
ACE-inhibitor/ARB	69 (86.3)	91 (93.8)	0.089
Diuretics	74 (92.5)	84 (86.8)	0.207
Aldosteron-antagonist	23 (28.8)	57 (58.8)	<**0.001**
Digitalis	16 (20.0)	20 (20.6)	0.919

LVEDD – left ventricular end-diastolic diameter, NYHA – New York Heart Association, AV-block – atrioventricular block, ACE – angiotensin converting enzyme, ARB – angiotensin receptor blocker.
Bold indicates a p-value of <0.05.
[a] Risk factors as proposed by Goldenberg et al. (age > 70 years, renal insufficiency, atrial fibrillation, NYHA class >2 and QRS duration >120 ms).

Table 2
Procedural and follow-up data of the two study groups. Continuous variables are displayed as mean ± standard deviation, categorical variables as number and percentage of the study group.

Procedural data and follow-up	CRT-P group	CRT-D group	p-Value
Operation time, min	89 ± 43	91 ± 33	0.703
Device-related complications, n (%)	4 (5.0)	9 (9.3)	0.458
Pericardial effusion	2 (2.5)	0 (0)	
Lead-revision	2 (2.5)	5 (5.2)	
Device-related infection	0 (0)	3 (3.1)	
Pocket hematoma	0 (0)	1 (1.0)	
Follow-up, months	23.5 ± 17.7	27.6 ± 19.8	0.152
Death, n (%)	28 (35.0)	34 (35.1)	0.994

3.3. Procedural data and adverse events

De-novo CRT implantation was successfully completed in all study patients. There was no significant difference in procedure time between the two groups. Procedure-related adverse events occurred in 13 of 177 study patients (7%) with a trend towards more complications in the CRT-D group (9% vs. 5%; p = ns) (Table 2). Lead dislodgement requiring a revision procedure was the most common major complication. Three percent of the CRT-D patients experienced device-related infections with the need of system removal during follow-up.

3.4. Outcome

3.4.1. Death from any cause

During a mean follow-up of 26 ± 19 months, 62 (35%) of the 177 study patients died, 28 (35%) in the CRT-P and 34 (35.1%) in the CRT-D group (hazard ratio, 1.16; 95% CI, 0.70 to 1.92; p = 0.563) (Table 2). Relevant clinical covariates possibly affecting survival (age, sex, LV-EF, type of cardiomyopathy, and number of risk factors) showed no significant influence on all-cause mortality in univariate analysis. The Kaplan-Meier analysis of survival probability found no significant difference between the two treatment groups (log-rank test, ns; p = 0.562) (Fig. 1). The estimated mean survival time was 45 months (95% CI, 38 to 53) for patients implanted with CRT-P and 51 months (95% CI, 43 to 59) for CRT-D respectively. This finding remained after adjustment for clinical relevant covariates in a multivariable Cox-regression model (hazard ratio, 0.98; 95% CI, 0.51 to 1.88; p = 0.952), which was used after successful testing for the proportional hazards assumption. The effects of CRT-D therapy in eight prespecified subgroups are illustrated in Fig. 2. No significant interaction effects between subgroup and treatment were identified.

3.4.2. Arrhythmic events and ICD interventions

During follow-up, 9 of the 97 patients in the CRT-D group (9.3%) experienced ICD interventions. Five patients (5.2%) had appropriate therapies (shocks in 3 and ATP in 2 patients), and 4 patients (4.1%) had inappropriate interventions (shocks in 3 and ATP in 1 patient) due to misclassification of a supraventricular arrhythmia. One patient in the CRT-P group (1%) experienced sustained VT and was upgraded to CRT-D.

4. Discussion

This observational study is the first to compare mortality between patients with an established indication for CRT and primary preventive ICD therapy implanted with either a CRT-D or CRT-P. Our study shows no additional survival benefit of ICD therapy in CRT recipients aged 75 years or older. In such an aged population sudden cardiac death from life-threatening arrhythmias is less common since life expectancy in the elderly is more likely limited by advanced heart failure and other comorbidities.

The COMPANION trial [7] showed a significant survival benefit for CRT, which was even greater in patients treated with a CRT-D, but the trial was not designed to detect differences in survival between CRT-P and CRT-D. Moreover, elderly patients were underrepresented (mean age 67 years), which does not allow to transfer the observed results to an aged population with shorter life-expectancy. On the other hand, implantation of a CRT-P, as compared to optimal medical therapy, was not only associated with a significant reduction in the risk of death from

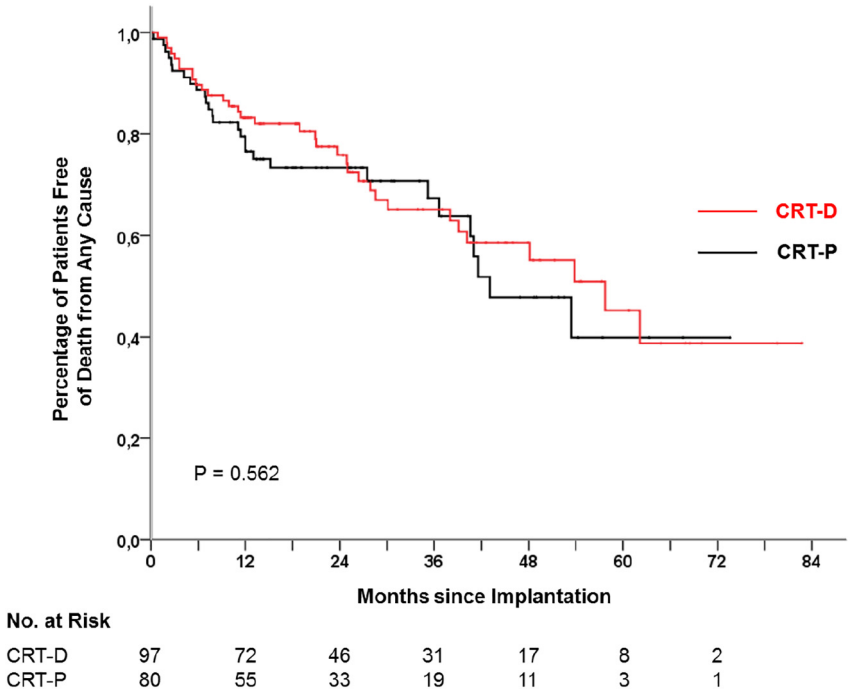

Fig. 1. Cumulative survival of patients implanted with a CRT-D device and patients implanted with a CRT-P device. Log-rank test, not significant (unadjusted p = 0.562). CRT – cardiac resynchronization therapy, ICD – implantable cardioverter-defibrillator, CRT-P – CRT-pacemaker, CRT-D – CRT-defibrillator.

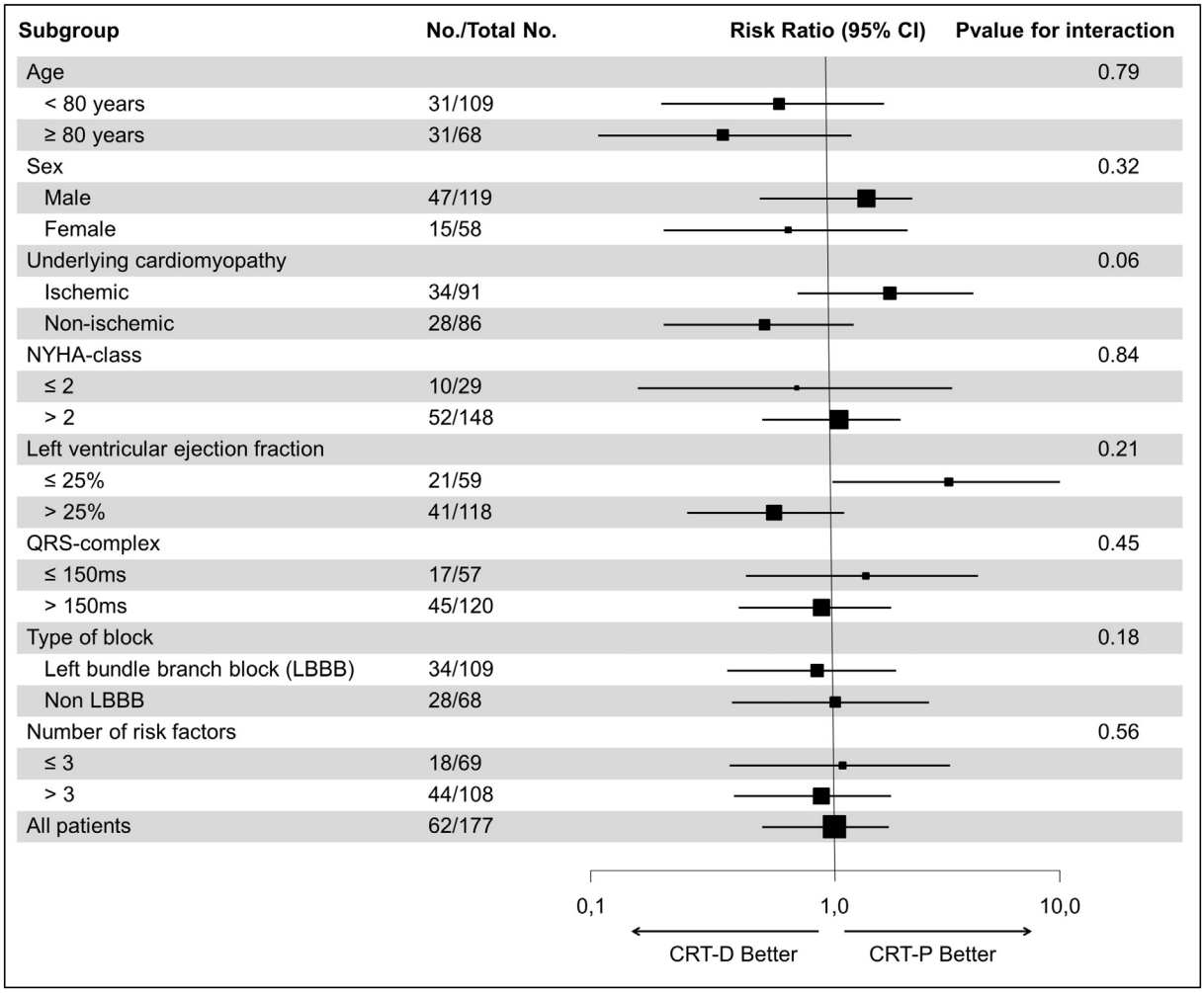

Fig. 2. Risk of death from any cause, according to selected clinical characteristics. The hazard ratios for death are shown for various subgroups among patients who received cardiac-resynchronization therapy with (CRT-D) and without (CRT-P) an implantable cardioverter-defibrillator. The horizontal lines indicate 95% confidence intervals. No subgroup treatment interactions were identified. All interaction p values exceeded 0.05.

heart failure but also in the risk of sudden death during an extended follow-up in the CARE-HF trial [17].

To help identify patients who may benefit from primary preventive ICD therapy, Goldenberg et al. [2] analyzed the MADIT II study population and developed a simple clinical risk score. In the presence of ≥3 risk factors (age, NYHA functional class, BUN, atrial fibrillation, and QRS duration) non-arrhythmic mortality predominated and defibrillator therapy was shown to be less effective. This risk score has been derived from ischemic patients with prior myocardial infarction, but application to non-ischemic patients with highly impaired LV systolic function seems to be reasonable, since the rate of sudden cardiac death is even lower in this population [18].

A recent study analyzed the survival benefit of primary preventive ICD therapy in older patients [19] by pooling data from 5 clinical trials and showed a survival benefit for patients treated with an ICD, but this was attenuated with increasing age. This finding was explained by the small sample size, higher burden of comorbid illness, and rising competing causes of death in elderly patients. Furthermore the authors did not provide information on the above mentioned and evaluated clinical risk factors of their patient population.

There are limited and contradictory data derived from different studies whether the addition of an ICD bears survival benefit in patients implanted with a CRT device. In a large single-center experience Kutyifa et al. showed that CRT-D was associated with a significant mortality benefit compared with CRT-P in heart failure patients with ischemic cardiomyopathy but not in those with non-ischemic cardiomyopathy [20]. On the other hand, a study based on a multivariate analysis of the MADIT-CRT [21] data, showed that patients older than 75 years experienced significantly less ventricular arrhythmias and appropriate ICD shocks than those younger than 75 years [22]. These findings support our data in questioning the benefit of an additional ICD in elderly patients. Another substudy of the MADIT-CRT trial, comparing the outcome after CRT implantation in different age groups, showed a reduction of heart failure events in all age groups, but mortality was only reduced in the group of patients aged 60–74 years and not in elderly patients [23].

The European CRT survey evaluated 2.438 patients implanted with a CRT device with or without an ICD in different European countries between November 2008 and June 2009 [24]. Similarly to our study, patients implanted with an ICD were younger, more often male and had more often ischemic cardiomyopathy. On short term follow-up, patients implanted with a CRT-D had improved survival compared to patients implanted with a CRT-P. However, the survey did not focus on elderly patients and overall patients were much younger than in our cohort (CRT-D patients: 68 versus 78 years; CRT-P patients: 75 versus 83 years). Furthermore the authors did not provide data on comorbidity burden or on the above mentioned risk factors.

The recently published French CeRtiTuDe cohort study [25] analyzed the cause of death in CRT-P versus CRT-D patients. Comparable with the results of our study, CRT-P patients in this multicenter prospective

follow-up cohort study were significantly older, less often male, more symptomatic with less coronary artery disease and had more comorbidities. The mortality rate among CRT-P patients was double compared with CRT-D, which was mainly due to non-sudden death. The authors concluded that this patient cohort with a mean age of 76 years would potentially not benefit from the addition of an ICD to CRT.

A systematic review and meta-analysis of 19 studies compared all-cause mortality between patients receiving CRT-D versus CRT-P [26]. The authors stated that the addition of an ICD is associated with a reduction in the risk of all-cause mortality, but most analyzed studies were cohort studies with significant differences in clinical characteristics between device groups. Overall, CRT-P patients were older, had more advanced heart failure, and a higher comorbidity burden. Therefore, these non-randomized studies are influenced by selection bias, and caution should be exercised in interpretation of these mortality data in favor of the CRT-D system.

The same author group applied the Goldenberg risk-score in CRT recipients in a retrospective observational cohort study in patients with ischemic or non-ischemic dilated cardiomyopathy and implanted CRT-D or CRT-P device. They found no survival benefit of the additional defibrillator in patients with a risk-score ≥ 3 [27]. These results certainly support our findings.

Apart from these clinical aspects, combined resynchronization and ICD therapy was shown to be cost-effective only in the subgroups of younger patients or those with high risk of sudden cardiac death [12].

Our observational study is the first to compare mortality between elderly patients with an established indication for CRT and primary preventive ICD therapy. The results are provocative, as the additional defibrillator seems to have no mortality benefit in this patient cohort, which is partially in line with the results of other observational trials but still not in accordance with the prevailing clinical routine. There is a need for better risk stratification to identify those patients who may have a survival benefit from defibrillator therapy as add-on to CRT, and on the other hand recognize patients well treated with CRT-P even in the presence of a potential indication for primary preventive ICD therapy.

4.1. Limitations

The major limitations of our study are imposed by its retrospective nature. Patients were not prospectively randomized to either treatment. Decision to implant a CRT-P or CRT-D device was taken at the discretion of the treating cardiologist, considering the patients' age and comorbidities among others. However, despite this selection bias, survival did not significantly differ between groups. Moreover, we do not provide detailed information on the mode of death (sudden versus non-sudden), since not all deaths were witnessed and devices not routinely interrogated posthumously. Hence, data on the biventricular device function at the time of death were not routinely recorded. Though CRT devices were regularly followed in the outpatient clinic, the rare instant of an acute HF-related death due to device malfunction cannot be entirely excluded. Our study was not powered to prove the non-inferiority of the CRT-pacemaker, but to refute the superiority of the CRT-defibrillator. The sample size of 177 patients allowed for a 96% power to detect a 20% difference in all-cause mortality between the treatment groups after 2 years of follow up.

5. Conclusions

Cardiac resynchronization therapy is an excellent treatment option for elderly patients with symptomatic heart failure, who represent a large proportion of the patients implanted with CRT devices nowadays. The results of our study support the hypothesis, that an additional ICD has no impact on survival in this patient cohort. A randomized controlled trial is certainly needed to validate our findings.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

MD, ME, ND, AM, KB, HK, MK, GH, and SR received research grants from Boston Scientific, Biotronik and St. Jude Medical.

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