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

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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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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).