Indian Pacing and Electrophysiology Journal 19 (2019) 4–6

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

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

Cardiac resynchronization therapy pacemakers versus defibrillators in older non-ischemic cardiomyopathy patients

Yanting Wang, Michael S. Sharbaugh, Andrew D. Althouse, Suresh Mulukutla, Samir Saba*

Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

ARTICLE INFO

Article history:
Received 2 August 2018
Accepted 14 August 2018
Available online 16 August 2018

Keywords:
Cardiac resynchronization therapy
Non-ischemic cardiomyopathy
Pacemaker
Defibrillator
Mortality

ABSTRACT

Introduction: With the recent publication of the negative DANISH trial, the mortality benefit of the implantable cardioverter-defibrillator (ICD) has been put in question in patients with non-ischemic cardiomyopathy (NICM). Because a majority of patients in DANISH receive cardiac resynchronization therapy (CRT) devices, we investigated in the present study the survival of recipients of CRT pacemakers (CRT-P) versus CRT ICDs (CRT-D) in a cohort of older (≥75 years) NICM patients at our institution.
Methods: A total of 135 NICM patients with CRT device were identified (42 with CRT-P and 93 with CRT-D) and were followed to the endpoint of all-cause mortality. Overall survival was compared between the CRT-P and CRT-D groups with adjustment for differences in baseline characteristics.
Results: Over a median follow-up of 46 months from the time of CRT device implantation, there were 54 total deaths (40%): 14 in the CRT-P (33%) and 40 in the CRT-D (43%) groups. Overall, CRT-P recipients had similar unadjusted mortality compared to CRT-D recipients (hazard ratio [HR] 1.04, 95% confidence interval [CI] 0.56–1.93), and this remained unchanged after adjusting for unbalanced covariates (HR 0.95, 95% CI 0.47–1.89) including left ventricular ejection fraction, used of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, and the Charlson comorbidity index.
Conclusion: Our data support that in older NICM patients with CRT devices, the addition of ICD therapy does not improve survival.

1. Introduction

With the recent publication of the negative DANISH trial [1], the mortality benefit of the implantable cardioverter-defibrillator (ICD) has been put in question in non-ischemic dilated cardiomyopathy (NICM) patients, despite it being recommended as a class I indication in this population according to the 2017 ACC/AHA/HRS guideline publication on management of patients with ventricular arrhythmias and prevention of sudden cardiac death [2]. Of note, 58% of all patients in the DANISH trial received cardiac resynchronization therapy (CRT) both in the ICD (CRT-D) and control (CRT-P) arms. Although subgroup analysis did not find a difference in the relative benefit of ICD therapy by CRT status [1], DANISH raises the question as to how much additional survival benefit the ICD provides over CRT in patients with NICM. In addition, subgroup analyses of DANISH [1] suggested that, in older patients in particular, ICD therapy has no incremental survival. Based on these data, the goal of our present study was to examine whether older NICM patients implanted with a CRT-D have decreased all-cause mortality compared to those implanted with a CRT-P device.

2. Methods

To study the effect of adding defibrillator to CRT in NICM patients, we analyzed patients who had undergone CRT device implantation between March 2002 and May 2013 at the University of Pittsburgh Medical Center hospitals. Patients were followed until death or last clinical encounter before December 21, 2015. The institutional review board of the University of Pittsburgh approved the study and the need for informed consent was waived. Patients with history of myocardial infarction, prior surgical or interventional revascularization, and significant coronary artery disease classified by >75% obstructive lesion in 1 main coronary artery, or 2 or more epicardial vessel were excluded. In addition, patients with any prior history of sustained ventricular arrhythmias were

* Corresponding author. University of Pittsburgh Medical Center, 200 Lothrop Street, South Tower 352.6, Pittsburgh, PA, 15213, USA.
E-mail address: sabas@upmc.edu (S. Saba).
Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2018.08.002

excluded. Patients were placed on guideline directed medical therapy unless clinically contraindicated or poorly tolerated. All patients were aged ≥75 years, had New York Heart Association Class III/IV heart failure symptoms, QRS ≥120 m s, and left ventricle ejection fraction (LVEF) ≤35%. Baseline demographic and clinical characteristics at the time of CRT device implantation were abstracted from electronic medical records. The Charlson co-morbidity index [3] was calculated for all patients.

Baseline characteristics of patients were expressed as mean ± standard deviation for continuous variables, which were compared using the student *t*-test, and as number (percentage) for discrete variables, which were compared using the chi square test. Survival was compared between CRT-P and CRT-D recipients using Kaplan-Meier curves. A multivariate Cox proportional-hazards model was used to estimate the mortality difference between CRT-P and CRT-D recipients while accounting for unbalanced baseline variables or other variables of clinical impact on all-cause mortality: pre-implant LVEF, rate of use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), and the Charlson co-morbidity index.

3. Results

A total of 135 NICM patients with CRT device were identified (42 with CRT-P and 93 with CRT-D). Table 1 details the baseline characteristics of the overall population stratified by type of CRT device implanted. There were no significant differences in age, pre-implant serum creatinine level, QRS duration on the surface electrocardiogram, prevalence of diabetes mellitus, hypertension, or in the calculated Charleston Comorbidity index. Compared to CRT-P recipients, CRT-D patients had however lower baseline LVEF (24.1 ± 6.42 vs. 28.0 ± 5.50, p = 0.002) and higher usage of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) (87.1% vs. 52.4%, p < 0.001).

The median follow-up for the overall cohort was 46 months from the time of CRT device implantation. Over this period, there were 54 total deaths (40%), including 14 in the CRT-P (33%) and 40 in the CRT-D (43%) groups. Overall, CRT-P recipients had similar unadjusted mortality compared to CRT-D recipients (hazard ratio [HR] 1.04, 95% confidence interval [CI] 0.56–1.93). This analysis remained unchanged after adjusting for unbalanced covariates (HR 0.95, 95% CI 0.47–1.89) (Fig. 1).

4. Discussion

Our results suggest that adding ICD therapy to CRT recipients with NICM aged 75 years or older may not be associated with improved survival. It is established that patients with NICM are less likely to experience fatal arrhythmias and more likely to respond to CRT than patients with ischemic cardiomyopathy [4,5]. With improved myocardial function in response to CRT, the rates of ventricular arrhythmias are also known to decrease significantly [6], which would minimize any potential added benefit from ICD therapy. In addition, it is well established that in first time recipients of ICDs, the rates of appropriate ICD shocks decrease dramatically with every decade of age [7]. All of these mechanisms form the conceptual model that explains why CRT-P may be equivalent to CRT-D in its effect on mortality in older NICM patients.

Still today, CRT guidelines do not distinguish between CRT-P and CRT-D devices although these two types of devices are very different [2]. CRT-P devices are smaller in size and therefore require a smaller incision for implantation. They also have a longer battery longevity, are less likely than CRT-D to be the subject of recall or advisory and cost a fraction of the cost of the defibrillator. Based on all these data, if in fact all-cause mortality is equivalent in older NICM recipients of CRT-P and CRT-D, then implanting preferentially CRT-P devices, would significantly reduce the healthcare cost of

Table 1
Baseline characteristics of the study population.

	TOTAL	CRT-P	CRT-D	P-value
# Patients	135	42	93	
Age at Implant (years)	81.0 ± 4.11	81.6 ± 5.26	80.7 ± 3.47	0.25
Atrial Fibrillation	107 (79.3%)	36 (85.7%)	71 (76.3%)	0.25
Congestive Heart Failure	119 (88.1%)	30 (71.4%)	89 (95.7%)	0.0003
Hypertension	95 (70.4%)	26 (61.9%)	69 (74.2%)	0.33
Diabetes mellitus	33 (24.4%)	8 (19.0%)	25 (26.9%)	0.42
Peripheral Vascular Disease	14 (10.4%)	6 (14.3%)	8 (8.6%)	0.26
Cerebrovascular Event	15 (11.1%)	4 (9.5%)	11 (11.8%)	0.78
Dementia	5 (3.7%)	3 (7.1%)	2 (2.2%)	0.13
Chronic Obstructive Pulmonary Disease	25 (18.5%)	10 (23.8%)	15 (16.1%)	0.21
Connective Tissue Disease	2 (1.5%)	0 (0.0%)	2 (2.2%)	0.35
Chronic Kidney Disease	4 (3.0%)	2 (4.8%)	2 (2.2%)	0.37
Leukemia	1 (0.7%)	1 (2.4%)	0 (0.0%)	0.12
Lymphoma	7 (5.2%)	4 (9.5%)	3 (3.2%)	0.10
Solid Tumor	35 (25.9%)	9 (21.4%)	26 (28.0%)	0.54
Charlson Comorbidity Index	3.82 ± 1.75	4.28 ± 2.15	3.63 ± 1.52	0.051
Left Ventricular Ejection Fraction (%)	25.2 ± 6.40	28.0 ± 5.50	24.1 ± 6.42	0.002
Left Ventricular End-Systolic Volume (mm)	45.0 ± 10.1	41.3 ± 10.1	46.4 ± 9.76	0.023
Left Ventricular End-Diastolic Volume (mm)	54.9 ± 9.03	51.2 ± 7.61	56.2 ± 9.18	0.013
Mitral Regurgitation				0.78
Mild	62 (45.9%)	18 (42.9%)	44 (47.3%)	
Moderate	38 (28.1%)	11 (26.2%)	27 (29.0%)	
Severe	19 (14.1%)	4 (9.5%)	15 (16.1%)	
Serum Creatinine (mg/dL)	1.33 ± 0.53	1.30 ± 0.43	1.34 ± 0.57	0.68
QRS Width (ms)	157 ± 28.3	152 ± 34.8	159 ± 24.9	0.21
Beta-Blocker	104 (77.0%)	31 (73.8%)	73 (78.5%)	0.71
ACE-I/ARB	103 (76.3%)	22 (52.4%)	81 (87.1%)	<0.001
Aldosterone Agonist	15 (11.1%)	2 (4.8%)	13 (14.0%)	0.12
Amiodarone	23 (17.0%)	6 (14.3%)	17 (18.3%)	0.55

ACE-I/ARB = Angiotensin Converting Enzyme inhibitor/Angiotensin Receptor Blocker.

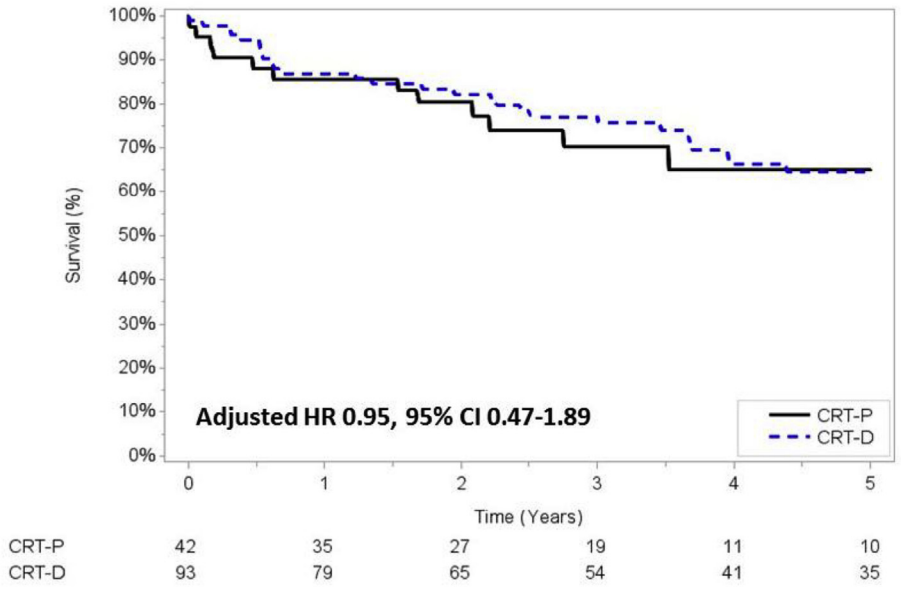

Fig. 1. Kaplan-Meier curve for survival in CRT-P vs CRT-D Recipients. Cardiac resynchronization therapy with pacemaker (CRT-P); cardiac resynchronization therapy with defibrillator (CRT-D).

managing these patients.

The present analysis has limitations. First, its small sample size and its single center, retrospective, observational design may introduce inherent biases. We corrected for these potential biases using multivariate statistical adjustments and the results were consistent for both the unadjusted and adjusted models. In addition, the cause of death could not be ascertained in most patients in this dataset.

Our results support the main findings of the DANISH trial, which suggest that in the presence of a CRT device, ICD therapy may not portend further survival benefit, in older NICM patients. This highlights the need for a pivotal, non-inferiority, randomized control, trial of CRT-P versus CRT-D in this population. Additionally, careful consideration of patients' goals, comorbidities, and frailty measures are essential when prescribing CRT-D or CRT-P in this population.

Disclosures

Drs. Wang, Sharbaugh, Althouse and Mulukutla have no disclosures to make; Dr. Saba discloses research support from NHLBI, Boston Scientific and Medtronic.

References

[1] Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S, DANISH Investigators. for the Danish Investigators. Defibrillation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–30.

[2] Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. AHA/acc/hrs guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. J Am Coll Cardiol 2017. 2017 Oct 30 [E-pub ahead of print], https://doi.org/10.1161/CIR.0000000000000548.

[3] Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–83.

[4] Barsheshet A, Goldenberg I, Moss AJ, Eldar M, Huang DT, McNitt S, Klein HU, Hall WJ, Brown MW, Goldberger JJ, Goldstein RE, Schuger C, Zareba W, Daubert JP. Response to preventive cardiac resynchronization therapy in patients with ischemic and nonischemic cardiomyopathy in MADIT-CRT. Eur Heart J 2011;32:1622–30.

[5] García-Lunar I, Castro-Urda V, Toquero-Ramos J, Mingo-Santos S, Moñivas-Palomero V, Daniela Mitroi C, Sánchez-García M, Pérez-Pereira E, Delgado HE, Fernández-Lozano I. Ventricular arrhythmias in super responders in cardiac resynchronization. Rev Esp Cardiol 2014;67:883–9.

[6] Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, Yong PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003;42:1454–9.

[7] Saba S, Adelstein E, Wold N, Stein K, Jones P. Influence of patients' age at implantation on mortality and defibrillator shocks. Europace 2017;19:802–7.