Published in final edited form as:

Pacing Clin Electrophysiol. 2016 August ; 39(8): 863–869. doi:10.1111/pace.12883.

The Effect of Chronic Kidney Disease on Mortality with Cardiac Resynchronization Therapy

David D. Daly Jr, MD, Arasi Maran, MD, J. Madison Hyer, MS, Frederick Funke, MD, Ashley Waring, MD, Frank Cuoco, MD, J. Lacy Sturdivant, MD, Robert B. Leman, MD, and Michael R. Gold, MD, PhD, FHRS

Abstract

BACKGROUND—Cardiac resynchronization therapy (CRT) improves functional status, reduces heart failure (HF) hospitalizations and decreases mortality. Several co-morbidities including renal function affect outcomes with CRT. However, moderate to severe chronic kidney disease (CKD) was an exclusion criteria in the large randomized control trials.

OBJECTIVE—To evaluate the association of renal function on survival following CRT implantation.

METHODS—This was a retrospective analysis of 432 consecutive patients implanted with an ICD with CRT (CRT-D). The primary endpoint was defined as death by any cause, and it was determined using hospital records and the United States Social Security Death Index. A Kaplan Meier analysis was performed separating renal dysfunction into renal stage based on glomerular filtration rate. Multivariate analysis was performed to assess the clinical predictors of mortality.

RESULTS—Patients were followed for up to 12 years with a mean follow up time of 4.3 ± 3.2 years. A total 164 patients (39.3 %) died over the course of the study. Patients with normal and mild renal disease (Stages 1 and 2) had improved survival compared with those with moderate, severe, or end stage (Stages 3–5) renal disease. This effect remained statistically significant after multivariate analysis. The estimated five year mortality was 36.3% for stage 1, 33.4 % for stage 2, 40.6% for stage 3, and 62.1% for stage 4/5 kidney disease ($p = 0.004$ by log rank test).

CONCLUSION—CKD is strong and independent predictor of long term mortality among patients undergoing CRT-D implantation.

Keywords

Implantable cardioverter-defibrillator; Cardiac Resynchronization Therapy; Chronic Kidney Disease; Kidney Disease Stage; Mortality

Corresponding Author: Michael R. Gold, MD, PhD, Division of Cardiology, Medical University of South Carolina, Charleston, SC, USA, Address for Correspondence: Medical University of South Carolina, 114 Doughty Street, MSC 592, Charleston, South Carolina, 29425-5920, Phone: (843) 876-4760 goldmr@musc.edu Fax: (843) 876-4990.

Author contributions: David Daly: research design, data acquisition, drafting of paper. Arasi Maran: data acquisition, drafting of paper. Fredrick Funke: data acquisition, drafting of paper. Ashley Waring: data acquisition, drafting of paper. Fran Cuoco: drafting of paper. Lacy Sturdivant: drafting of paper. Robert Leman: drafting of paper. Michael Gold: research design, data acquisition, drafting of paper.

INTRODUCTION

The prevalence of chronic kidney disease (CKD) continues to increase (1–3), and it is associated with a high risk for sudden cardiac death (2,4,5). Although the mechanisms underlying this increased risk are likely multifactorial, it is well established that the sympathetic nervous system is hyperactive in patients with CKD and the common associated co-morbidities of hypertension and congestive heart failure. (6–9). In support of a potential causal relationship, plasma norepinephrine levels among patients with chronic renal disease are an independent predictor of survival and cardiovascular events (10).

The implantable cardioverter-defibrillator (ICD) with or without cardiac resynchronization therapy (CRT) has been shown to improve survival in select patient populations; however, moderate to severe CKD was an exclusion criteria in the large randomized control trials studying CRT or ICD placement (11–14). Retrospective studies have suggested that CKD is associated with mortality after ICD implantation, but much less is known regarding survival following CRT (15–18). Accordingly, the present study was designed to evaluate that relationship between the stage of renal dysfunction and mortality in a large cohort of patients undergoing CRT patients.

METHODS

Study Design

This was a retrospective cohort study from a prospective database of consecutive patients implanted with an ICD with CRT (CRT-D) for primary or secondary prevention from 2002 to 2011 at the Medical University of South Carolina. The primary endpoint was all cause mortality. This study was approved by the MUSC IRB and all patients gave informed consent for device implantation.

Data Collection

The study cohort included 432 consecutive patients who underwent CRT-D implantation during the study period. Of these, 15 were excluded due to insufficient data. The remaining 417 patients were included in the analyses. Co-morbid conditions were defined as those existing at the time of device implantation. Left ventricular ejection fraction (EF) was determined primarily by two-dimensional echocardiography, but when necessary by left ventriculography, or cardiac nuclear imaging. Classification of heart failure was based on the New York Heart Association functional class. Date of death was determined using hospital records and the United States Social Security Death Index.

Measurement of Renal Function

A pre-implantation serum creatinine level closest to the date of device implantation was used to calculate renal function. Patient weight, height age and race were used to calculate the estimated glomerular filtration rate (eGFR ml/min/1.73m²) using the Modified Diet in Renal Dysfunction equation (19). The eGFR was then used to categorize patients into a corresponding stage of CKD 1 (eGFR>90ml/min/1.73m²), 2 (eGFR=60–89 ml/min/

1.73m²), 3 (eGFR=30–59 ml/min/1.73m²), 4 (eGFR=15–30 ml/min/1.73m²), and 5 (eGFR<15ml/min/1.73m² or on dialysis).

Statistical Analysis

Descriptive statistics are presented for all demographic, exposure, and comorbidities in the form of frequency (%) and mean $\pm$ standard deviation for discrete and continuous variables, respectively. Differences between renal stages were assessed using Chi-square and analysis of variance (ANOVA) tests for discrete and continuous variables, respectively.

Prior to investigating covariates, time-to-event analysis was performed using Kaplan-Meier estimates and a log-rank test. Two Cox proportional hazards models were constructed to assess the relationships between our primary predictors (renal stage and eGFR) and mortality, while adjusting for all relevant covariates. Each covariate's impact on mortality was assessed independently, and all that were significantly associated with mortality were entered into multivariable models along with the primary predictor. Then, a backwards-stepwise approach was taken to identify a final model. In all models, the proportional-hazards assumption was assessed and was found to not be violated.

Time = 0 was defined as date of device implantation. If no mortality record was found, survival time was censored at the last visit or patient contact by electronic medical record review. An α -level of 0.05 was considered statistically significant and p-values were not adjusted for multiple comparisons.

Results

Baseline Characteristics

The baseline characteristics of the study population patients are shown in Table 1. The cohort was predominately late middle age males with hypertension, advanced heart failure, and device placement for primary prevention.. There were several differences among the cohort grouped by CKD stage. With more advanced renal failure, patients tended to be older, have atrial fibrillation, and advanced heart failure (HF), while ACE inhibitor or angiotensin receptor blocker therapy was less common. Amiodarone use was more common in advanced renal failure likely due to concomitant atrial fibrillation, given the limited antiarrhythmic drugs that can be safely used in this scenario.

Mortality

Patients were followed for up to 12 years with a mean follow up time of 4.3 ± 3.2 years. A total of 163 (39.1 %) subjects died over the course of the study. The mortalities grouped by CKD stage are shown in Figure 1. The patients with normal and mild renal disease (Stages 1 and 2) had improved survival compared with those with moderate, severe, or end stage (Stages 3–5) renal disease. The estimated five year mortality was 36.3% for stage 1, 33.4 % for stage 2, 40.6% for stage 3, and 62.2% for stage 4/5 kidney disease ($p = 0.004$ by log rank test). By 10 years post-implantation, approximately 70 percent of the patients with stage IV or V CKD had died.

Peri-procedural mortality (death during the implant hospitalization or within 30 days of implant) occurred in only 3 patients (0.7%) in the study. Two of the patients had stage 3 CKD and one patient stage 5 CKD. None of these patients died from progressive renal failure or of a known complication of the implant procedure. One of the patients with stage 3 CKD was admitted with new onset heart failure and received a CRT-D device during his hospitalization before eventually expiring from progressive heart failure 18 days after his implantation. The second patient with stage 3 CKD underwent device implantation and was discharged 2 days after his procedure before he died 20 days later from unknown etiology. The third patient with stage 5 CKD had a history of sarcoidosis with conduction disease requiring frequent pacing and was admitted for knee replacement but developed PEA arrest during her orthopedic procedure. Her device was upgraded to a CRT-D shortly after the arrest due to concern of RV lead dysfunction but the patient's neurological status did not recover and she died due to anoxic brain injury 19 days after device implantation.

Many of the comorbidities associated with advanced renal failure are also associated with increased mortality such as age, HF class, hypertension and atrial fibrillation. Accordingly, a multivariate analysis of predictors of mortality was performed. This analysis showed that CKD Stage, QRS duration, ischemic heart disease, amiodarone use, and advanced heart failure (stage III or stage IV) were independent predictors of mortality (Table 2). Less severe CKD, longer QRS duration, non-ischemic cardiomyopathy, mild HF and absence of amiodarone use was associated with lower mortality. When compared to severe renal dysfunction (Stage IV/V), patients with normal GFR (Stage I) and with mildly reduced GFR (Stage II) have a 52 % and 56 % reduced risk of mortality respectively. Patients with moderate renal impairment (Stage III) have a 36% reduced risk of mortality.

Analyzing the effect of a continuous variable by grouping the population by pre-specified cutoffs can lose some granularity of the data and impact clinical predictors (20), Accordingly, the multivariate analysis was repeated with eGFR treated as a continuous variable. These results are shown in Table 3. Age is now an independent predictor of mortality. Moreover, for every 10 unit increase in GFR, there is a 6% decrease in mortality rate amongst the patient population.

DISCUSSION

This study evaluated the association of renal failure on survival following CRT-D implantation. To our knowledge this is the longest follow-up study of such a cohort allowing for accurate assessment of interaction of renal failure on the benefit of CRT in HF. The primary results of this study are that renal failure is a powerful and independent predictor of mortality. Patients with Stage IV/V CKD have a 62.2% 5-year mortality despite CRT with ICD backup, which is approximately the expected battery life of these devices (21,22). Thus, over half of advanced renal failure patients will die before needing a pulse generator replacement. The impact of CKD on survival was not restricted to just the Stage IV/V subgroup as there was a stepwise decline in survival based on the clinical stage of renal function, and estimated glomerular filtration rate was a strong independent predictor of mortality.

CKD is common among patients with underlying cardiovascular disease, so this is an important clinical problem. However, patients with advanced renal failure are often excluded from clinical trials; thus, the optimal strategy for treating such subjects remains unclear. CKD has been estimated to be present in one out of every seven adults in the United States, with only a small proportion of these subjects progress to renal replacement therapy (2). Comorbidities, especially cardiovascular disease, rise with the progressive decline of GFR and cardiovascular disease is proportionally the single largest contributor to death in ESRD patients (23,24). Moreover, ESRD patients who survive sudden cardiac death (SCD) have a survival rate as low as 15% at one year (7).

Prior studies have demonstrated a high mortality of ICD patients in the presence of CKD, which has led some to question the benefit of implanting such devices in end stage renal disease. However, the higher incidence of appropriate ICD shocks in the presence of renal insufficiency has led others to conclude that ICD therapy should not be withheld for this comorbidity (25,26). It is noteworthy that patients with impaired renal function have higher rates of complications during device placement, including lead related complications, infection, and bleeding (27,28), further confounding the decision process for treatment. Cuculich studied patients undergoing primary prevention ICD implantation. Those with CKD were more likely to receive ICD therapy, more likely to receive antiarrhythmic drugs, and over ten times more likely to die during follow up period versus those with normal renal function (29).

Wase identified a $GFR < 60$ as a predictor of mortality and specifically arrhythmic deaths (24). In comparison to death by any other cause, there was a significantly higher rate of arrhythmic death in those subjects with CKD as compared to those with $GFR \geq 60$. A trend toward higher defibrillation thresholds in those with CKD raised the possibility that failed shocks contributed to arrhythmic death. In contrast, we observed no effect of CKD on defibrillation threshold.

The impact of CRT on mortality in renal failure patients is likely more complex, but has been less well studied. In addition to protecting patients from arrhythmic death, CRT can improve cardiac function and hemodynamics which likely contributes to renal failure. Adestein et al studied about 800 patients in whom CRT was planned and compared successful implants to patients who LV lead placement was not successful. In this study, the patients with a GFR less than 30 ml/min had no survival benefit and no change in echocardiographic indicators of CRT response (30). A prior observational study showed that a GFR of less than 60 ml/min was associated with increased mortality compared to the general population but results were not stratified by clinically relevant CKD stage (17). Conversely, studies suggest that patients with mild to moderate renal dysfunction may have improvement in cardiac, renal dysfunction, and possibly mortality with CRT (31).

A decision model for primary prevention ICD implantation identified age and CKD as predictors of poor survival after ICD implantation (32). Our study suggests that renal failure does not show a threshold relationship with mortality as it is modeled in most studies. Rather mortality rates increase progressively as renal dysfunction increases from mild to moderate to severe. This is a similar observation to that noted with QRS duration and CRT, where

dichotomizing populations at an arbitrary cutoff (e.g. 150 msec) can obscure the continuous relationship with outcomes (33). Given the conflicting data with regard to survival and arrhythmic events in CKD, it remains unclear if device therapy improves outcomes in this population. This will likely only be resolved by randomized controlled trials.

LIMITATIONS

The study should be interpreted in light of certain methodologic limitations. This was a retrospective analysis so is subject to potential bias in the inclusion of subjects. Consecutive patients were included to try to mitigate this limitation. All-cause mortality was the primary end point rather than cardiovascular or arrhythmia related death. However, prior studies looking at arrhythmia related deaths also found a similar trend toward CKD as an independent predictor of mortality for this endpoint. Moreover, classifying etiology of death in heart failure patients is challenging, particularly in the presence of renal failure (34). A detailed history of device therapy is not available. Finally, there were a relatively small number of patients with Stage IV and Stage V CKD.

CONCLUSIONS

In summary, CKD is an independent predictor of long term mortality among patients underlying CRT-D implantation. There is no obvious threshold for this effect as mortality increases as CKD progresses. The clinical importance of this effect is evident by the multivariate analysis showing a 6% change in mortality with a 10 ml/min/1.73 m² change in GFR. The high mortality observed with CKD Stage IV/V patients supports the need for controlled trials to assess the benefit of both ICD and CRT-D in this population.

Acknowledgments

FUNDING SOURCES

This study was funded in part by the South Carolina Clinical and Translational Research Institute (SCTR Award UL1 TR001450).

Disclosures: Dr. Gold has received research grants and served as a consultant to Boston Scientific, St Jude and Medtronic. He has received research grants from Boston Scientific and has received honoraria from Boston Scientific, Medtronic and Biotronik. Dr Cuoco has received research grants from Medtronic and honoraria from St Jude.

ABBREVIATIONS

CRT	Cardiac resynchronization therapy
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
HF	Heart Failure
ICD	Implantable cardioverter-defibrillator

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CLINICAL PERSPECTIVE

Patients with moderate to severe renal disease have been poorly studied in device trials. Given the increased mortality of patients with this degree of renal dysfunction after CRT implantation, it remains unclear if CRT improves survival in this population. Randomized clinical trials are needed to evaluate this complex patient population after device implantation.

Figure 1. Relationship between renal function and mortality. Kaplan-Meier curves of mortality with the cohort grouped by Renal Stage is shown.

Table 1

Baseline Patient Characteristics by Renal Stage Class.

Variable	Total N = 415	Stage I N = 44	Stage II N = 162	Stage III N = 179	Stage IV/V N = 30	p-value
Death (%)	163 (39.1%)	15 (34.1%)	52 (32.1%)	78 (43.6%)	18 (60.0%)	0.013
Age	67.3 ± 10.2	61.5 ± 11.7	65.9 ± 9.3	69.7 ± 9.8	68.7 ± 10.3	<0.001
Female (%)	116 (27.8%)	13 (29.5%)	43 (26.5%)	52 (29.1%)	7 (23.3%)	0.89
BSA	2.0 ± 0.2	2.1 ± 0.3	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.3	0.43
LVEF	25.4 ± 7.5	25.9 ± 9.6	24.8 ± 7.2	25.4 ± 6.7	28 ± 9.6	0.19
DFT (Joules)	10.8±6.3	10.5±6.2	10.5±5.7	11.1±6.5	11.1±7.8	0.82
NYHA III/IV HF (%)	359 (86.1%)	32 (72.7%)	136 (84.0%)	161 (89.9%)	28 (93.3%)	0.014
Ischemic (%)	253 (60.7%)	23 (52.3%)	92 (56.8%)	114 (63.7%)	23 (76.7%)	0.10
Secondary Prevention (%)	56 (13.5%)	11 (19.3%)	11 (6.6%)	29 (17.1%)	5 (22.7%)	0.008
QRS Duration (ms)	155.7 ± 23.6	153.6 ± 23.3	155.7 ± 24.7	156.4 ± 21.7	154.4 ± 29.6	0.90
LBBB (%)	236 (57.0%)	24 (54.5%)	93 (57.4%)	102 (57.6%)	15 (51.7%)	0.93
Hypertension (%)	278 (66.7%)	26 (59.1%)	104 (64.2%)	128 (71.5%)	18 (60.0%)	0.26
Diabetes (%)	153 (36.6%)	15 (34.1%)	53 (32.7%)	71 (39.7%)	13 (43.3%)	0.48
Atrial Fibrillation (%)	40 (9.7%)	1 (2.3%)	16 (9.9%)	16 (9.0%)	7 (24.1%)	0.021
Beta Blocker (%)	361 (86.4%)	37 (84.1%)	144 (88.9%)	152 (84.9%)	25 (83.3%)	0.66
ACE Inhibitor/ARB (%)	332 (79.6%)	36 (81.8%)	142 (87.7%)	131 (73.2%)	21 (70.0%)	0.005
Amiodarone (%)	48 (11.5%)	2 (4.5%)	18 (11.1%)	23 (12.8%)	5 (16.7%)	0.36

BSA = body surface area; LVEF = left ventricular ejection fraction

Table 2

Results of multivariable analysis of Renal Stage and Clinical Factors on mortality.

Parameter	Comparison	Hazard Ratio	95% CI	p
Renal Stage I	Renal Stage IV/V	0.48	0.22–1.03	0.059
Renal Stage II	Renal Stage IV/V	0.44	0.24–0.82	0.010
Renal Stage III	Renal Stage IV/V	0.64	0.36–1.16	0.141
Age	Per 1year	1.02	1.00–1.04	0.018
Ischemic	Ischemic vs. non-ischemic	1.75	1.22–2.52	0.002
QRS Duration	Per 1ms	0.99	0.98–1.00	0.001
Advanced Heart Failure	Advanced HF vs. Mild HF	2.81	1.45–5.45	0.002
Amiodarone	Amiodarone vs. Not	1.85	1.24–2.78	0.003

CI = confidence interval; QRS = ; ms = milliseconds; HF = heart failure

Table 3

Results of multivariable analysis of eGFR and Clinical Factors on mortality.

Parameter	Comparison	Hazard Ratio	95% CI	p
eGFR	Per 10 ml/min/1.73m ²	0.94	0.87–1.02	0.129
Age	Per 10 years	1.20	1.02–1.42	0.032
Ischemic	Ischemic vs. Non-ischemic	1.90	1.31–2.75	< 0.001
QRS Duration	Per 1 ms	0.99	0.98–1.00	0.001
Advanced Heart Failure	Advanced HF vs. Mild HF	2.86	1.48–5.52	0.002
Amiodarone	Amiodarone vs. Not	1.72	1.13–2.63	0.011

CI = confidence interval; QRS = ; ms = milliseconds; HF = heart failure