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Comparative Effectiveness of CRT-D Versus Defibrillator Alone in HF Patients With Moderate-to-Severe Chronic Kidney Disease

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ABSTRACT

BACKGROUND Patients with moderate-to-severe chronic kidney disease (CKD) are poorly represented in clinical trials of cardiac resynchronization therapy (CRT).

OBJECTIVES This study sought to assess the real-world comparative effectiveness of CRT with defibrillator (CRT-D) versus implantable cardioverter-defibrillator (ICD) alone in CRT-eligible patients with moderate-to-severe CKD.

METHODS We conducted an inverse probability-weighted analysis of 10,946 CRT-eligible patients (ejection fraction <35%, QRS >120 ms, New York Heart Association functional class III/IV) with stage 3 to 5 CKD in the National Cardiovascular Data Registry (NCDR) ICD Registry, comparing outcomes between patients who received CRT-D (n = 9,525) versus ICD only (n = 1,421). Outcomes were obtained via Medicare claims and censored at 3 years. The primary endpoint of heart failure (HF) hospitalization or death and the secondary endpoint of death were assessed with Cox proportional hazards models. HF hospitalization, device explant, and progression to end-stage renal disease were assessed using Fine-Gray models.

RESULTS After risk adjustment, CRT-D use was associated with a reduction in HF hospitalization or death (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.78 to 0.91; $p < 0.0001$), death (HR: 0.85; 95% CI: 0.77 to 0.93; $p < 0.0004$), and HF hospitalization alone (subdistribution HR: 0.84; 95% CI: 0.76 to 0.93; $p < 0.009$). Subgroup analyses suggested that CRT was associated with a reduced risk of HF hospitalization and death across CKD classes. The incidence of in-hospital, short-term, and mid-term device-related complications did not vary across CKD stages.

CONCLUSIONS In a nationally representative population of HF and CRT-eligible patients, use of CRT-D was associated with a significantly lower risk of the composite endpoint of HF hospitalization or death among patients with moderate-to-severe CKD in the setting of acceptable complication rates. (J Am Coll Cardiol 2015;66:2618–29)

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Advanced symptomatic heart failure (HF) and chronic kidney disease (CKD) are frequently comorbid and represent 2 of the most challenging and costly diseases for individuals, families, and societies. Approximately 60% of Medicare patients with HF have stage 3 or greater CKD (1). Annual HF expenditures in the United States are approximately $30 billion, and this is expected to rise to $53 billion by 2030 (2). Although improvements in HF care via pharmacological neurohormonal modulation have improved longevity and quality of life for the overall population of HF patients, these therapies are often contraindicated, poorly tolerated, or of reduced efficacy among patients with advanced CKD.

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Over the past decade, cardiac resynchronization therapy (CRT) has emerged as an important therapy for patients with a prolonged QRS and moderate-to-severe medication-refractory systolic HF. Multiple large randomized trials have demonstrated that CRT can reduce HF symptoms, HF hospitalizations, and death (3–6). These landmark studies either excluded or did not report outcomes among patients with advanced (stages 3b to 5) CKD (7). Data on CRT in advanced CKD are currently limited to small, retrospective, single-center studies (8,9) and a single meta-analysis (10). Concerns regarding the potential for decreased CRT efficacy and increased complications may lower the rate of CRT use in patients with advanced CKD. Thus, optimal device strategy for this population remains unclear (11) and variability in practice exists (12).

To address this important gap in knowledge, we performed an observational comparative effectiveness analysis comparing outcomes among CRT-eligible patients who received a CRT with implantable cardioverter-defibrillator (ICD) versus ICD alone in the National Cardiovascular Data Registry (NCDR) ICD Registry. We hypothesized that CRT would be associated with a lower risk in HF hospitalizations and death, but the magnitude of effect may be attenuated based on severity of CKD.

METHODS

DATA SOURCES. NCDR ICD Registry. Patients for this study were selected from the NCDR ICD Registry, a national registry that included approximately 90% of all ICD implantations in the United States (13). All Medicare beneficiaries receiving a primary prevention ICD are enrolled in the ICD registry according to a mandate from the Centers for Medicare & Medicaid Services. The ICD registry includes extensive information on baseline patient characteristics and in-hospital outcomes. Rigorous data abstraction processes and standards have been published and include electronic data submission via a secure website, standardized variable definitions, electronic quality checks, and annual on-site audits of 10% of enrolling sites (14). This approach has led to >90% accuracy for data elements (15).

Medicare database. Longitudinal outcomes were obtained by linking fee-for-service Medicare claims to the ICD registry using a previously validated methodology (16) with indirect identifiers: hospital, patient sex, birth date, admission date, and discharge date. Inpatient claims, outpatient claims, and the denominator files were used to assess morbidity and mortality. We used the Chronic Conditions Warehouse database (years 2005 to 2011), which includes both Part A and Part B Medicare claims to assess specific covariates and outcomes.

STUDY POPULATION. We restricted the study population to all fee-for-service Medicare patients ≥65 years old with stage 3 to 5 CKD (glomerular filtration rate [GFR] <60 ml/min/1.73 m^2, including those on dialysis) who underwent ICD implantation (with or without CRT) between January 1, 2006, and December 31, 2009; were eligible for CRT based on contemporary indications during the study period (ejection fraction [EF] <35%, QRS >120 ms, New York Heart Association [NYHA] functional class III/IV); and could be linked to Medicare claims data. We excluded patients who were admitted during a non-elective hospitalization, were enrolled in the ICD registry at the time of generator change, required an epicardial lead, or had a prior pacemaker or defibrillator.

PATIENT CHARACTERISTICS. All baseline characteristics except for the frailty and dementia variables were directly obtained from the ICD registry case report form. Dementia was defined by the presence of a diagnosis from either of 2 Hierarchical Condition Categories (HCCs): "dementia" or "senility, nonpsychotic organic brain syndromes/conditions." Frailty/disability was defined by the following HCCs: protein-calorie malnutrition; quadriplegia, other extensive paralysis; paraplegia; spinal cord disorders/injuries; hemiplegia/hemiparesis; legally blind; decubitus ulcer of skin; chronic ulcer of skin, except decubitus; vertebral fractures; amputation status, lower limb amputation; and amputation status, upper limb. Missing variables were addressed with the multiple imputation technique; the coefficients of

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CKD = chronic kidney disease

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy with defibrillator

EF = ejection fraction

ESRD = end-stage renal disease

GFR = glomerular filtration rate

HCC = Hierarchical Condition Categories

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

ICD-9 = International Classification of Diseases-Ninth Revision-Clinical Modification

LBBB = left bundle branch block

NYHA = New York Heart Association

5 rounds of imputation were combined to obtain the final estimates for the models.

GFR was calculated using the Modification of Diet in Renal Disease formula (17). For subgroup analyses, patients were divided based on CKD stage: 3a (GFR 45 to 59 ml/min/1.73 m^2), 3b (GFR 30 to 44 ml/min/1.73 m^2), 4 (GFR 15 to 29 ml/min/1.73 m^2), and 5 (GFR <15 ml/min/1.73 m^2 or on dialysis).

TREATMENT. The treatment of interest was CRT with ICD (CRT-D) versus ICD alone as defined by the ICD registry.

OUTCOMES. The primary outcome was the composite endpoint of HF hospitalization or death. Secondary outcomes included HF hospitalization, death, progression to end-stage renal disease (ESRD), device explant, and in-hospital and short-term out-of-hospital complications. Follow-up was censored 3 years after device implant or on the date at which the patient's data were no longer available (due to death or transition to a managed care plan).

Vital status was determined by the Medicare denominator file. Longitudinal outcomes were determined by International Classification of Diseases-Ninth Revision-Clinical Modification (ICD-9)-CM, Current Procedural Terminology (CPT) codes, or diagnosis related group (DRG) codes as appropriate: HF hospitalization (DRG 127 before October 1, 2007, and DRGs 291 to 293 on or after October 1, 2007); device explant (both CPT 33241 and 33244). Incident transition to ESRD was defined by the first occurrence of any ICD-9 code in the HCC "dialysis status" or selected ICD-9 codes from HCC "renal failure": 99656, 99656, 99673, V451, V4511, V4512, V560, V561, V562, V5631, V5632, V568, 40301, 40311, 40311, 40391, 40402, 40403, 40412, 40413, 40492, 40493, 5855, and 5856. Post-discharge complications included hemothorax or pneumothorax (ICD-9 codes 512.1, 511.8, 511.89), hematoma (ICD-9 code 998.1x), cardiac tamponade or pericardial effusion requiring pericardiocentesis (ICD-9 codes 420.x, 423.0, 423.3, or 423.9, or ICD-9 procedure codes 37.0 or 37.12), mechanical complications requiring system revision (ICD-9 codes 996.04 or 996.01 combined with ICD-9 procedure codes 37.75, 37.79, 37.97, 37.99, or 00.52), and device-related infection (ICD-9 code 996.61).

STATISTICAL ANALYSIS. Baseline characteristics of the study population by treatment group are described using proportions for categorical variables and means with standard deviations for continuous variables. Differences between groups were tested using the chi-square test for categorical variables and Student *t* tests for continuous variables.

We reported observed event rates by treatment group. For the primary endpoint of HF hospitalization or death and the secondary endpoint of death, we used the Kaplan-Meier methods to calculate event rates and log-rank test to assess differences between groups. For HF hospitalization, progression to ESRD, and device explant, we utilized the cumulative incidence function to calculate event rates and Gray tests to assess differences between groups. The cumulative incidence function accounts for the competing risk of mortality, which is high in this population.

To estimate the risk-adjusted association between CRT-D and each outcome, we employed inverse probability-weighted Cox proportional hazard or Fine-Gray models. We used logistic regression models to predict CRT-D use deriving an inverse probability weight based on the following covariates: age, sex, race, ethnicity, QRS duration, QRS morphology, cardiomyopathy etiology, atrial fibrillation or flutter, history of sustained ventricular arrhythmia, EF, NYHA symptom class, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior valve surgery, medication use (beta-blockers, aldosterone antagonists, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aspirin, statin, clopidogrel, ticlopidine, hydralazine, long-acting nitrate, amiodarone, warfarin, digoxin, diuretic), diabetes, prior myocardial infarction, sinus node dysfunction, chronic lung disease, cerebrovascular disease, systolic blood pressure, creatinine, blood urea nitrogen, dialysis dependence, serum sodium, prior cardiac arrest, hypertension, syncope, HF duration, atrioventricular conduction, CKD stage, implanting operator training, implanting operator volume, geographic region, teaching versus nonteaching hospital, hospital size, implant year, dementia, electrophysiology laboratory presence in hospital, and disability/frailty. The differences between these characteristics in the weighted ICD and CRT-D groups were examined by calculating absolute standardized differences. Small standardized differences (<10%) indicate that the baseline covariates among patients in the CRT-D and ICD alone groups are balanced.

Falsification endpoints (18) (gastrointestinal bleed [ICD-9 code 578] and bone disorder/fracture [ICD-9 codes 730 to 736, 802 to 824]) were chosen to test the adequacy of our statistical model because these outcomes should not vary based on the receipt of CRT-D versus ICD.

We subsequently assessed for an interaction between baseline characteristics (including CKD class) and the association between CRT-D and

outcomes with multivariable models with adjustment for all covariates in models; we adjusted for CKD in all models where CKD class was not the variable of interest. We reported hazard ratios (HR) or subdistribution HR and their 95% confidence intervals (CIs) based on robust sandwich variance estimates to account for clustering of patients within hospitals. A p value of <0.05 was considered statistically significant for all tests. Analyses were performed using SAS (version 9.3, SAS institute, Cary, North Carolina).

RESULTS

Between January 1, 2006, and December 31, 2009, 60,299 individuals with an EF <35% and QRS >120 ms underwent new ICD implantation and were enrolled in the registry; 64% (n = 38,274) of these individuals had stage 3 CKD or greater. We excluded individuals with mildly symptomatic HF (NYHA functional class I/II; n = 10,087), a prior pacemaker (n = 8,464), those implanted during a nonelective hospitalization (n = 8,466), and those who required an epicardial LV lead (n = 311), resulting in a total study population of 10,947. Median follow-up was 30 months. Baseline patient, hospital, operator, and procedure characteristics associated with receipt of CRT-D versus ICD are detailed in **Table 1**.

Logistic regression analyses (Online Table 1) demonstrate that receipt of CRT-D (vs. ICD) was more common among those with left bundle branch block (LBBB), longer QRS durations, having an electrophysiologist as the implanting physician, and higher volume of CRT implants at the hospital and physician level. CRT-D implantation was less common among those with atrial fibrillation or flutter, absence of a prior history of ventricular tachycardia, non-white race, and among those implanted early in the study period. There was no relationship between CKD stage, age, or sex, and likelihood of receiving a CRT-D versus ICD.

We assessed rates of in-hospital, 30-day, and 90-day complication rates across CKD subgroups. There was no significant difference in total in-hospital, 30-day, or 90-day complications among CRT-D or ICD recipients across CKD subgroups (**Table 2**). CRT-D implantation (vs. ICD alone) was not associated with an increased risk of in-hospital, 30-day, or 90-day complications.

Among all CRT eligible individuals, CRT-D use was associated with a lower 3-year incidence of HF hospitalization or death (57% vs. 45%; $p < 0.001$) (**Figure 1A**), death (40% vs. 31%; $p < 0.001$) (**Figure 1B**), HF hospitalization (37% vs. 29%; $p < 0.001$) (**Figure 1C**), but not progression to ESRD (CKD stages 3 and 4 only [n = 10,348]; 8% vs. 7%; p = 0.20) (**Figure 1D**) in unadjusted analyses. There were no differences in the rates of device explant or the falsification endpoints of gastrointestinal bleed and bone disorder/fracture. See **Table 3** for a complete display of unadjusted 3-year incidence rates and unadjusted models describing the relation between CRT-D (vs. ICD) and outcomes.

In inverse probability-weighted models, CRT-D use was associated with a significantly lower risk of HF hospitalization or death (HR: 0.82; 95% CI: 0.75 to 0.90; $p < 0.0001$), death (HR: 0.84; 95% CI: 0.76 to 0.94; p = 0.0019), and HF hospitalization (subdistribution HR: 0.81; 95% CI: 0.72 to 0.91; p = 0.0003), but not device explant, transition to ESRD (among CKD stages 3 and 4), or falsification endpoints (**Table 3**). Notably, the cohorts resulting from the inverse probability-weighted estimators analyses were well balanced with regard to baseline patient characteristics, demonstrating adequate statistical adjustment for all measured baseline characteristics (Online Table 2).

Subgroup analyses by CKD class demonstrated there were no significant interactions between treatment (CRT-D vs. ICD) and CKD class and the outcomes of HF hospitalization or death (p = 0.15), HF hospitalization (p = 0.13), and death (p = 0.69) (**Central Illustration**, Online Figure 1 for the associated unadjusted analyses).

We performed multivariable-adjusted subgroup analyses to assess for the presence of an interaction between device type, key baseline characteristics, and the primary outcome of HF hospitalization or death (**Figure 2**, Online Figure 2 for the associated unadjusted analyses). We noted no significant interaction between key baseline characteristics, device type, and outcomes, except for QRS morphology. We found a significant interaction between LBBB versus non-LBBB QRS morphology, device type, and the primary outcome ($p_{interaction} = 0.0005$), and subgroup analyses suggested that the lower risk of HF hospitalization or death occurred exclusively in the LBBB population (LBBB: 0.73, 95% CI: 0.66 to 0.81; $p < 0.0001$ vs. non-LBBB: 0.97, 95% CI: 0.86 to 1.09; p = 0.58). In an exploratory analysis, we found no interaction ($p_{interaction} = 0.67$) between QRS morphology, device type, and transition to ESRD. When subgroup analyses by CKD stage were performed in the LBBB-only population (Online Table 3), we found results similar to those found in the overall population (**Central Illustration**). There was no interaction between QRS duration, device type, and outcome.

TABLE 1 Baseline Patient, Hospital, Operator, and Procedure Characteristics

	ICD (n = 1,421)	CRT-D (n = 9,525)	p Value
Age, yrs	75.9 ± 6.1	75.7 ± 6.1	0.22
Sex			
Male	1,013 (71.3)	6,229 (65.4)	<0.0001
Female	408 (28.7)	3,296 (34.6)	
Race			
White non-Hispanic	1,217 (85.6)	8,464 (88.9)	0.0007
Black non-Hispanic	113 (8.0)	566 (5.9)	
Hispanic	64 (4.5)	296 (3.1)	
Other	27 (1.9)	199 (2.1)	
QRS duration, ms			
120–129	244 (17.2)	740 (7.8)	<0.0001
130–139	258 (18.2)	1,426 (15.0)	
140–149	245 (17.2)	1,751 (18.4)	
150–159	218 (15.3)	1,726 (18.1)	
160–169	205 (14.4)	1,739 (18.3)	
≥170	251 (17.7)	2,143 (22.5)	
Intraventricular conduction			
Missing	1 (0.1)	8 (0.1)	<0.0001
Abnormal—LBBB	745 (52.4)	7,016 (73.7)	
Abnormal—other	675 (47.5)	2,501 (26.3)	
Non-ischemic cardiomyopathy			
Missing	0 (0.0)	2 (0.0)	<0.0001
No	1,074 (75.6)	6,240 (65.5)	
Yes—within the past 9 months	103 (7.2)	904 (9.5)	
Yes—>9 months	244 (17.2)	2,379 (25.0)	
Ischemic heart disease	1,101 (77.5)	6,475 (68.0)	<0.0001
Atrial fibrillation/atrial flutter	559 (39.3)	3,164 (33.2)	<0.0001
Ventricular tachycardia	308 (21.7)	1,643 (17.2)	0.0002
NYHA functional class			
III	1,348 (94.9)	9,046 (95.0)	0.86
IV	73 (5.1)	479 (5.0)	
Previous PCI	455 (32.0)	3,011 (31.6)	0.95
Previous CABG	719 (50.6)	3,968 (41.7)	<0.0001
Previous valvular surgery	123 (8.7)	792 (8.3)	0.70
Diabetes	626 (44.1)	4,060 (42.6)	0.56
Previous myocardial infarction	856 (60.2)	5,047 (53.0)	<0.0001
Sinus node function			
Missing	1 (0.1)	5 (0.1)	<0.0001
Normal	991 (69.7)	7,177 (75.3)	
Abnormal	429 (30.2)	2,343 (24.6)	
Chronic lung disease	350 (24.6)	2,335 (24.5)	0.92
Cerebrovascular disease	287 (20.2)	1,557 (16.3)	0.0013
Cardiac arrest	35 (2.5)	163 (1.7)	0.12
Hypertension	1,154 (81.2)	7,570 (79.5)	0.17
Syncope	170 (12.0)	928 (9.7)	0.0318
CHF duration			
Missing	0 (0.0)	2 (0.0)	<0.0001
No	98 (6.9)	213 (2.2)	
<9 months	347 (24.4)	2,328 (24.4)	
>9 months	976 (68.7)	6,982 (73.3)	

Continued in the next column

TABLE 1 Continued

	ICD (n = 1,421)	CRT-D (n = 9,525)	p Value
AV conduction			
Missing	5 (0.4)	33 (0.3)	0.14
Normal	937 (65.9)	6,572 (69.0)	
First degree heart block	432 (30.4)	2,621 (27.5)	
Second or third degree (not paced)	47 (3.3)	299 (3.1)	
EF, %	23.8 (5.7)	23.3 (5.8)	0.0024
CKD stage			
3a	698 (49.1)	4,721 (49.6)	0.0004
3b	444 (31.2)	3,171 (33.3)	
4	168 (11.8)	1,146 (12.0)	
5	111 (7.8)	487 (5.1)	
Dialysis	100 (7.0)	417 (4.4)	<0.0001
BUN level, mg/dl			
Missing	2 (0.1)	11 (0.1)	0.0331
≤20	245 (17.2)	1,962 (20.6)	
20–40	869 (61.2)	5,607 (58.9)	
>40	305 (21.5)	1,945 (20.4)	
Sodium level, mEq/l			
Missing	4 (0.3)	30 (0.3)	0.55
≤135	204 (14.4)	1,291 (13.6)	
135–145	1,187 (83.5)	8,067 (84.7)	
>145	26 (1.8)	137 (1.4)	
Systolic BP, mm Hg			
Missing	12 (0.8)	41 (0.4)	0.10
≤100	90 (6.3)	653 (6.9)	
100–130	603 (42.4)	4,184 (43.9)	
>130	716 (50.4)	4,647 (48.8)	
Angiotensin-converting enzyme inhibitor	827 (58.2)	5,367 (56.3)	0.19
Amiodarone	194 (13.7)	1,148 (12.1)	0.09
Hydralazine	81 (5.7)	494 (5.2)	0.42
Angiotensin receptor blocker	259 (18.2)	2,048 (21.5)	0.0048
Aspirin	948 (66.7)	6,383 (67.0)	0.82
Beta-blocker	1,200 (84.4)	8,217 (86.3)	0.06
Warfarin	423 (29.8)	2,646 (27.8)	0.12
Digoxin	379 (26.7)	2,648 (27.8)	0.37
Diuretic	1,105 (77.8)	7,574 (79.5)	0.13
Long-acting nitrate	193 (13.6)	1,354 (14.2)	0.52
Clopidogrel	337 (23.7)	2,150 (22.6)	0.34
Ticlopidine	9 (0.6)	36 (0.4)	0.16
Statin	952 (67.0)	6,268 (65.8)	0.38
Dementia	45 (3.2)	289 (3.0)	0.79
Disability/frailty	131 (9.2)	704 (7.4)	0.0155
EP operator ICD training			
Unknown	411 (28.9)	2,368 (24.9)	<0.0001
Board-certified EP/EP fellowship	703 (49.5)	5,850 (61.4)	
Surgeon	23 (1.6)	70 (0.7)	
Other	284 (20.0)	1,237 (13.0)	
Operator CRT volume			
≤20 implants/year	986 (69.4)	4,841 (50.8)	<0.0001
>20 implants/year	435 (30.6)	4,684 (49.2)	

Continued on the next page

TABLE 1 Continued

	ICD (n = 1,421)	CRT-D (n = 9,525)	p Value
Region			
Other	54 (3.8)	278 (2.9)	0.17
New England	55 (3.9)	408 (4.3)	
Atlantic	477 (33.6)	3,171 (33.3)	
Central	680 (47.9)	4,465 (46.9)	
Mountain	55 (3.9)	380 (4.0)	
Pacific	100 (7.0)	823 (8.6)	
Teaching status			
Unknown	53 (3.7)	278 (2.9)	0.21
Council of teaching hospitals	386 (27.2)	2,742 (28.8)	
Teaching hospital	385 (27.1)	2,635 (27.7)	
Not teaching hospital	597 (42.0)	3,870 (40.6)	
Center CRT volume			
≤20 implants/yr	324 (22.8)	1,059 (11.1)	<0.0001
>20 implants/yr	1,097 (77.2)	8,466 (88.9)	
Beds set up and staffed			
Unknown	53 (3.7)	278 (2.9)	0.0011
≤100	70 (4.9)	532 (5.6)	
101-500	883 (62.1)	5,488 (57.6)	
>500	415 (29.2)	3,227 (33.9)	
Implant year			
2006	383 (27.0)	2,149 (22.6)	<0.0001
2007	384 (27.0)	2,362 (24.8)	
2008	366 (25.8)	2,544 (26.7)	
2009	288 (20.3)	2,470 (25.9)	
EP lab present in hospital	994 (70.0)	6,671 (70.0)	0.95

Values are mean ± SD or n (%).

AV = atrioventricular; BP = blood pressure; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CHF = congestive heart failure; CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; EF = ejection fraction; EP = electrophysiologist/electrophysiology; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

DISCUSSION

In this observational study of CRT-eligible individuals with stages 3 to 5 CKD, we demonstrated that CRT-D use was associated with a significantly lower risk of HF hospitalization or death, death, and HF hospitalization. Subgroup analyses demonstrated no interaction between treatment (CRT-D vs. ICD) and CKD class and death or HF hospitalization. In the setting of nonsignificant interaction terms, it appears that the absence of an association (based on point estimates) between CRT-D receipt and lower risk of death among CKD stage 5 patients and a lower risk of HF hospitalizations among CKD V and IV patients is related to insufficient power (Online Table 4). There was no association between CRT-D use and progression to ESRD (among CKD stages 3 and 4) and device explant. In-hospital, short-term, and mid-term complications associated with CRT implantation do not appear to vary based on CKD stage. Notably, a significant association between CRT-D use and lower risk of the primary outcome (HF hospitalization or death) was observed exclusively in LBBB patients. Otherwise, the association between CRT-D use and outcomes did not vary based on key baseline characteristics: age, sex, NYHA functional class, CKD class, ejection fraction, QRS duration, cardiomyopathy etiology, diabetes, or atrial fibrillation or flutter. To date, this represents the largest study of patients with advanced CKD undergoing CRT and supports the use of CRT independent of renal function.

IN THE CONTEXT OF THE CURRENT LITERATURE. Although retrospective analyses of landmark CRT trials have shown an association between CRT and improved outcomes in patients with mild-to-moderate CKD, until now, analyses of patients with more advanced (stages 3b to 5) CKD have been limited to small, single-center studies and a single meta-analysis. In a pre-specified analysis of the CARE-HF study (Cardiac Resynchronization–Heart Failure Study), CRT was associated with a similar reduction in death or cardiovascular hospitalization among individuals with a GFR <60 ml/min/1.73 m^2 and those with a GFR >60 ml/min/1.73 m^2 (4). Similarly, a subgroup analysis of the RAFT trial (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial) (which included NYHA functional class II/III patients) demonstrated that the favorable impact of CRT did not vary based on a GFR threshold of 60 ml/min/1.73 m^2 (6). A secondary analysis of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study (which included NYHA functional class I/II patients) demonstrated that although echocardiographic response was worsened among individuals with a GFR <60.3 ml/min/1.73 m^2, the risk reduction associated with CRT did not vary based on this GFR threshold (19). It is important to note that these landmark trials either formally excluded or did not report enrollment of patients with more advanced CKD.

Although the few retrospective studies that exist suggest that CRT may have a role in advanced CKD (8,10,20), these studies have been small, single-centered, and often without a control group. Not surprisingly, a recent authoritative review on the evidence for HF therapies in CKD concluded that although there are data to support the use of CRT in CKD stage 3, there are no specific data to guide its use in CKD stages 4 and 5 (11). Importantly, the results

TABLE 2 Complications Associated With CRT-D and ICD Implantation Across CKD Stages

	Device	All (CKD Stages 3-5) (n = 10,946)	CKD Stage 3a (n = 5,419)	CKD Stage 3b (n = 3,615)	CKD Stage 4 (n = 1,314)	CKD Stage 5 (n = 598)	p_{trend}*	$p_{interaction}$†
In-hospital complications								
Any	ICD	82 (5.8)	36 (5.2)	29 (6.5)	9 (5.4)	8 (7.2)	0.70	0.51
	CRT	571 (6.0)	278 (5.9)	197 (6.2)	74 (6.5)	22 (4.5)	0.44	
Death	ICD	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0.45	0.75
	CRT	23 (0.2)	9 (0.2)	6 (0.2)	6 (0.5)	2 (0.4)	0.13	
Hematoma	ICD	33 (2.3)	15 (2.1)	15 (3.4)	1 (0.6)	2 (1.8)	0.22	0.23
	CRT	239 (2.5)	111 (2.4)	84 (2.6)	35 (3.1)	9 (1.8)	0.39	
Pneumothorax or hemothorax	ICD	15 (1.1)	6 (0.9)	6 (1.4)	2 (1.2)	1 (0.9)	0.86	0.54
	CRT	90 (0.9)	53 (1.1)	23 (0.7)	10 (0.9)	4 (0.8)	0.34	
Cardiac tamponade or pericardial effusion requiring pericardiocentesis	ICD	13 (0.9)	8 (1.1)	1 (0.2)	2 (1.2)	2 (1.8)	0.15	0.10
	CRT	58 (0.6)	27 (0.6)	23 (0.7)	7 (0.6)	1 (0.2)	0.55	
30-day complications								
Any 30-day complication‡	ICD	67 (4.7)	31 (4.4)	23 (5.2)	7 (4.2)	6 (5.4)	0.63	0.57
	CRT	474 (5.0)	234 (5.0)	160 (5.0)	64 (5.6)	16 (3.3)	0.28	
Hematoma	ICD	43 (3.0)	20 (2.9)	17 (3.8)	3 (1.8)	3 (2.7)	0.58	0.53
	CRT	302 (3.2)	139 (2.9)	106 (3.3)	45 (3.9)	12 (2.5)	0.26	
Pneumothorax or hemothorax	ICD	17 (1.2)	7 (1.0)	7 (1.6)	2 (1.2)	1 (0.9)	0.85	0.51
	CRT	104 (1.1)	61 (1.3)	27 (0.9)	12 (1.0)	4 (0.8)	0.28	
Cardiac tamponade or pericardial effusion requiring pericardiocentesis	ICD	16 (1.1)	8 (1.1)	2 (0.5)	4 (2.4)	2 (1.8)	0.12	0.07
	CRT	87 (0.9)	43 (0.9)	32 (1.0)	11 (1.0)	1 (0.2)	0.38	
90-day complications								
Any 90-day complication§	ICD	5 (0.4)	3 (0.4)	2 (0.5)	0 (0.0)	0 (0.0)	1.00	0.84
	CRT	31 (0.3)	16 (0.3)	11 (0.3)	3 (0.3)	1 (0.2)	1.00	
Mechanical complications requiring a system revision	ICD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n/a	n/a
	CRT	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00	
Device-related infection	ICD	5 (0.4)	3 (0.4)	2 (0.5)	0 (0.0)	0 (0.0)	1.00	0.84
	CRT	31 (0.3)	16 (0.3)	11 (0.3)	3 (0.3)	1 (0.2)	1.00	

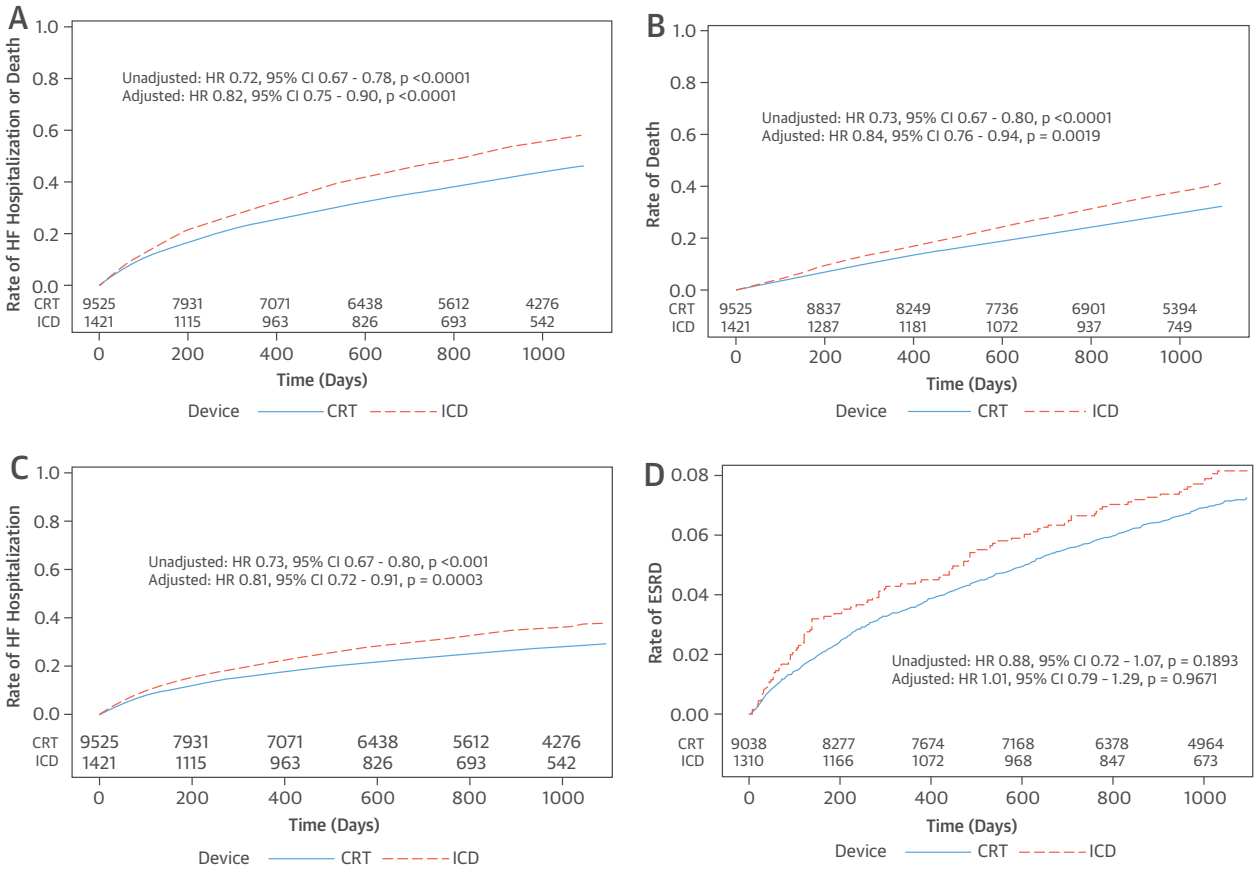
Values are n (%). *Trend across CKD stages, within designated device category. †Between device type and outcome, within the overall population. ‡Hematoma, pneumothorax, and tamponade or pericardial effusion requiring pericardiocentesis. §Mechanical complications, device infection.

Abbreviations as in Table 1.

from the current study corroborate the observed association between CRT and improved outcomes in stage 3 CKD and, importantly, demonstrate the extension of these benefits to the population of patients with stages 4 and 5 CKD.

Prior analyses of CRT in CKD have demonstrated that CRT may have the potential to improve renal function (8,21,22). Although the potential improvement in GFR as assessed by a recent meta-analysis appears to be small (~2.3 ml/min/1.73 m^2), a significant minority may experience improvements sufficient to reclassify the CKD stage (10). Furthermore, some studies have suggested that as CKD increases in severity, the likelihood of an appreciable improvement in GFR increases (8,21). On the basis of these data, we hypothesized that CRT may have the potential to reduce the transition to ESRD among stage 3 and 4 CKD patients. In our study, we found no relationship between treatment type and progression to ESRD. There are many potential reasons for this finding. First, it is possible that CRT-induced changes in cardiorenal physiology are simply too incremental or not sufficiently sustained to influence a hard endpoint such as transition to ESRD. It is also possible that patients with stage 3 and 4 CKD are too far along in the process of renal deterioration to experience CRT-induced reduction in the risk of progression to ESRD. It is also possible that a lack of statistical power or insufficient follow-up precluded our ability to detect an existing relationship between CRT and a reduction in progression to ESRD. Notably, it remains possible that individuals with a milder degree of renal impairment may experience delayed or reduced progression to ESRD.

FIGURE 1 Rates of HF Hospitalization or Death, Death, HF Hospitalization, and Progression to ESRD Among Patients With CRT-D Versus ICD Alone



Kaplan-Meier curves are shown for heart failure (HF) hospitalization or death **(A)** and death **(B)**. Cumulative incidence functions accounting for the competing risks of death for HF hospitalization **(C)** and progression to end-stage renal disease (ESRD) **(D)** are shown. CI = confidence interval; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; HR = hazard ratio; ICD = implantable cardioverter-defibrillator.

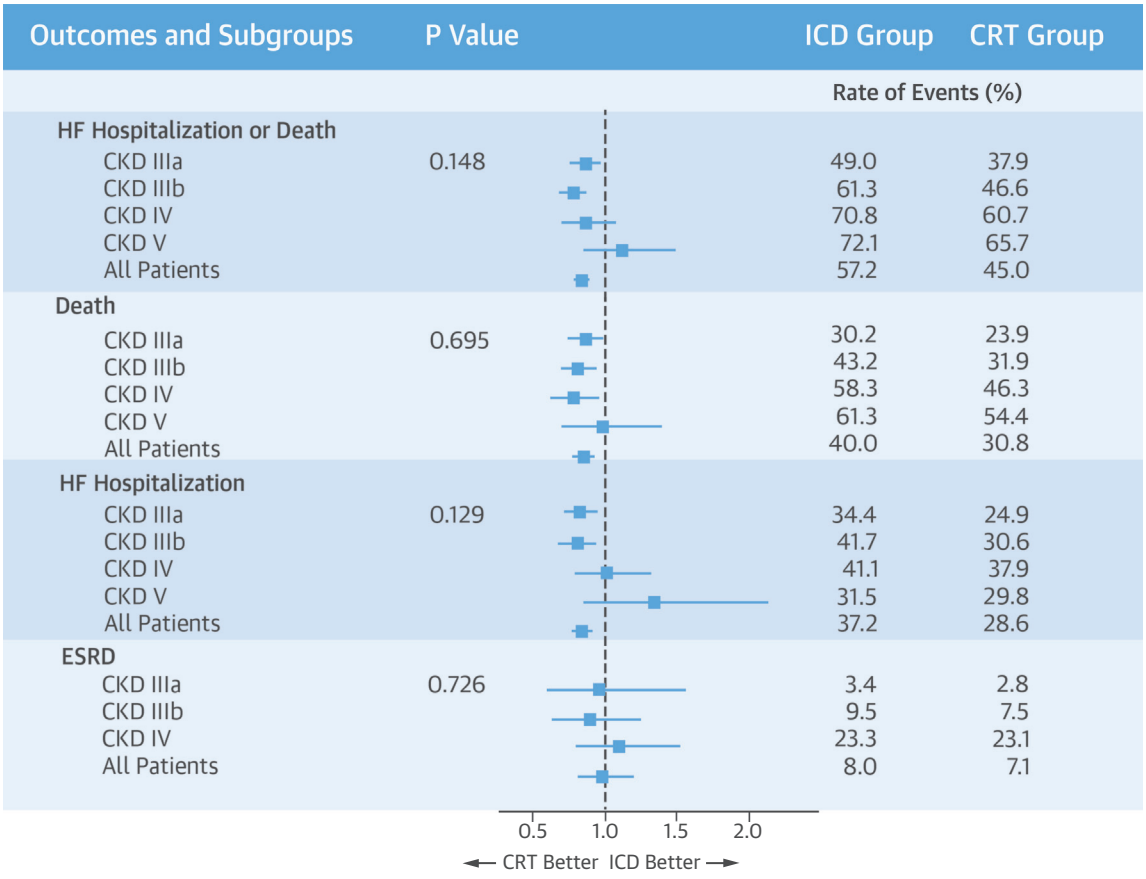
TABLE 3 Unadjusted 3-Year Event Rates and Unadjusted and Adjusted Analyses Comparing Outcomes Among CRT-D and ICD Recipients

	Unadjusted 3-Year Event Rates		Unadjusted		Adjusted*	
Outcomes	ICD (n = 1,421)	CRT-D (n = 9,525)	HR or Subdistribution HR (95% CI) for CRT-D vs. ICD	p Value	HR or Subdistribution HR (95% CI) for CRT-D vs. ICD	p Value
HF hospitalization or death†	813 (57.2)	4,282 (45.0)	0.72 (0.67-0.78)	<0.0001	0.82 (0.75-0.90)	<0.0001
Death†	569 (40.0)	2,936 (30.8)	0.73 (0.67-0.80)	<0.0001	0.84 (0.76-0.94)	0.0019
HF hospitalization‡	529 (37.2)	2,722 (28.6)	0.73 (0.67-0.80)	<0.0001	0.81 (0.72-0.91)	0.0003
ESRD‡§	105 (8.0)	637 (7.0)	0.88 (0.72-1.07)	0.19	1.01 (0.79-1.29)	0.97
Device explant‡	4 (0.3)	19 (0.2)	0.72 (0.24-2.12)	0.54	0.64 (0.16-2.60)	0.53
Gastrointestinal bleed‡	169 (11.9)	1,121 (11.8)	0.99 (0.84-1.17)	0.92	1.11 (0.91-1.36)	0.30
Bone disorder/fracture‡	373 (26.2)	2,448 (25.7)	0.98 (0.88-1.09)	0.66	0.92 (0.80-1.04)	0.19

Values are n (%) unless otherwise noted. *Adjusted using inverse probability-weighted Cox proportional hazard or Fine-Gray models, as appropriate. †Hazard ratio. ‡Subdistribution hazard ratio. §For 10,348 pre-ESRD patients, including 9,038 CRT patients.

CI = confidence interval; ESRD = end-stage renal disease; HF = heart failure; HR = hazard ratio; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **CRT-D Versus ICD in Patients With Advanced CKD: Outcomes by CKD Stage**



Friedman, D.J. et al. J Am Coll Cardiol. 2015; 66(23):2618–29.

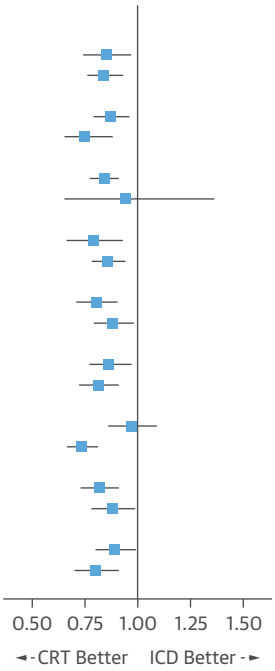
Hazard ratios (HR) were calculated for the endpoints of heart failure (HF) hospitalization or death and death. Subdistribution HR were calculated for the endpoints of HF hospitalization and transition to end-stage renal disease (ESRD). Confidence intervals (CI) are presented with each point estimate. CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; ICD = implantable cardioverter-defibrillator.

Prior studies have suggested that more severe renal dysfunction was associated with increased risk of device-related complications (23–25). These reports of increased complications may have influenced the reduced rates of CRT utilization among individuals with advanced CKD. In our study, we demonstrated that among CRT-D recipients, progressive CKD was not associated with an overall increased risk of in-hospital, 30-day, or 90-day complications.

STUDY LIMITATIONS. First, treatment was not randomized, and although we utilized sophisticated statistical methods to account for differences between treatment groups, we cannot rule out the potential for residual confounding. The ICD Registry does not include information on cardiac structure and function (except for EF), and thus we cannot exclude the possibility that differences in chamber size, valvular disease, dyssynchrony, and so on may have influenced device selection and outcomes. We do note that the lack of association between treatment group and the falsification endpoints and the well-balanced characteristics among the treatment groups in the cohorts resulting from the inverse probability-weighted estimator analyses suggest that statistical techniques were adequate. Our study population was limited to adults ≥65 years of age with fee-for-service Medicare, and thus, the results may not be generalizable to younger individuals. In contrast to randomized trials of CRT, we did not have access to echocardiographic data, and this study did not include patient-centered outcomes, including

FIGURE 2 **Forest Plot Depicting Multivariable-Adjusted Subgroup Analyses**

Subgroup	HR (95%CI)	P value	ICD Group No. Event	ICD Group No. Patient	ICD Group Rate (%)	CRT Group No. Event	CRT Group No. Patient	CRT Group Rate (%)
Age								
<75 Yr	0.85 (0.74-0.97)	0.942	327	595	55	1713	4160	41.2
>=75 Yr	0.84 (0.76-0.93)		486	826	58.8	2569	5365	47.9
Sex								
Male	0.87 (0.79-0.96)	0.114	593	1013	58.5	2997	6229	48.1
Female	0.75 (0.65-0.88)		220	408	53.9	1285	3296	39
NYHA class								
III	0.84 (0.77-0.91)	0.528	769	1348	57.1	3999	9046	44.2
IV	0.94 (0.65-1.36)		44	73	60.3	283	479	59.1
Ischemic Cardiomyopathy								
No	0.79 (0.66-0.93)	0.359	180	347	51.9	1241	3283	37.8
Yes	0.86 (0.78-0.94)		633	1074	58.9	3041	6242	48.7
Ejection Fraction								
<25%	0.80 (0.71-0.90)	0.227	377	597	63.2	2119	4411	48
>=25%	0.88 (0.79-0.98)		436	824	52.9	2163	5114	42.3
QRS Duration								
< 150ms	0.86 (0.77-0.97)	0.523	439	747	58.8	1944	3917	49.6
>= 150ms	0.81 (0.72-0.91)		374	674	54.5	2338	5608	41.7
Bundle Branch Morphology								
Non-LBBB	0.97 (0.86-1.09)	0.001	407	675	60.3	1416	2502	56.6
LBBB	0.73 (0.66-0.81)		406	746	54.4	2866	7023	40.8
Diabetes								
No	0.82 (0.73-0.91)	0.387	132	795	54.3	2259	5465	41.3
Yes	0.88 (0.78-0.99)		381	626	60.9	2023	4060	49.8
Atrial Fibrillation/Flutter								
No	0.89 (0.80-0.99)	0.224	460	862	53.4	2615	6361	41.1
Yes	0.80 (0.70-0.91)		353	559	63.2	1667	3164	52.7



The p-value is from the test statistic for testing the interaction between the device and any subgroup variable. The rate is the event rate.

The Forest plot depicts multivariable adjusted (for all covariates, including chronic kidney disease) subgroup analyses relating the association between device type (CRT-D vs. ICD alone), baseline characteristics, and the primary outcome of HF hospitalization or death. LBBB = left bundle branch block; NYHA = New York Heart Association; other abbreviations as in Figure 1.

measures of quality of life, functional status, and symptom burden. This study utilized registry data linked to administrative claims, and as such, the results may be adversely affected by inaccuracies in data collection and coding. The creatinine values used to calculate GFR were the last known values, and although we excluded patients implanted during an acute hospitalization, we cannot be certain that all creatinine values were truly representative of patients' baseline renal function. We did not have access to follow-up laboratory analyses and thus could not assess the relation between CRT-D use and changes in renal function that could be clinically relevant. Our study was limited to CKD patients who were felt suitable for ICD implantation and may not be generalizable to all CKD patients. There were fewer patients with stage 4 and 5 CKD (compared with stage 3), and as such, analyses of stage 4 and 5 patients were not powered to detect associations between device type and certain outcomes in our subgroup analyses. CRT-D was more often implanted at higher-volume CRT centers that may have superior medication management and outpatient follow-up; however, the ICD Registry includes a wide variety of sites, and we have adjusted for multiple site and physician-related factors. Finally, our study compared CRT-D versus ICD and thus we are unable to determine the relative efficacy of CRT-D compared with CRT with pacemaker or to medical management because patients managed without a defibrillator are not enrolled in the ICD Registry.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS. Current guidelines recommend CRT without particular regard to kidney function (26). However, individuals with advanced CKD may be less likely to receive CRT (12). The reasons for decreased CRT use are likely multifactorial, including concerns regarding increased risk of complications, decreased likelihood of clinical response, and increased competing causes of morbidity and mortality. Taken

in sum, the results from this study support the use of CRT independent of kidney function (particularly in LBBB patients) and similarly support the existing guideline recommendations. Importantly, CRT implantation appears to be safe in individuals with advanced CKD.

Future prospective studies on this topic are needed to confirm these results. Prospective studies measuring patient-centered outcomes are likely to improve our understanding of how CRT influences quality of life, functional status, and HF symptoms in CKD patients. This valuable information would allow for vast improvements in patient education and the shared decision-making process regarding whether or not to pursue CRT in this highly comorbid, symptomatic population.

CONCLUSIONS

In a nationally representative cohort of older patients with symptomatic HF and moderate to severe CKD, CRT-D was associated with a reduction in the risk of HF hospitalization and mortality, in the context of acceptable complication rates. These results should be confirmed by prospective randomized studies.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: CRT-D is associated with a lower risk of heart failure hospitalization or death among patients with stages 3 to 5 chronic kidney disease, including those on dialysis, than management with defibrillators alone.

TRANSLATIONAL OUTLOOK: Future studies should address the impact of CRT on such patient-oriented outcomes as quality of life, functional status, and mental health.

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KEY WORDS biventricular, cardiomyopathy, chronic kidney disease, pacemaker

APPENDIX For supplemental figures and tables, please see the online version of this article.