Comparative Effectiveness of Cardiac Resynchronization Therapy Among Patients With Heart Failure and Atrial Fibrillation

Findings From the National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry

Prateeti Khazanie, MD, MPH; Melissa A. Greiner, MS; Sana M. Al-Khatib, MD, MHS; Jonathan P. Piccini, MD, MHS; Mintu P. Turakhia, MD, MAS; Paul D. Varosy, MD; Frederick A. Masoudi, MD, MSPH; Lesley H. Curtis, PhD; Adrian F. Hernandez, MD, MHS; for the National Cardiovascular Data Registry

Background—Atrial fibrillation is common in patients with heart failure, but outcomes of patients with both conditions who receive cardiac resynchronization therapy with defibrillator (CRT-D) compared with an implantable cardioverter-defibrillator (ICD) alone are unclear.

Methods and Results—Using the National Cardiovascular Data Registry's ICD Registry linked with Medicare claims, we identified 8951 patients with atrial fibrillation who were eligible for CRT-D and underwent first-time device implantation for primary prevention between April 2006 and December 2009. We used Cox proportional hazards models and inverse probability-weighted estimates to compare outcomes with CRT-D versus ICD alone. Cumulative incidence of mortality (744 [33%] for ICD; 1893 [32%] for CRT-D) and readmission (1788 [76%] for ICD; 4611 [76%] for CRT-D) within 3 years and complications within 90 days were similar between groups. After inverse weighting for the probability of receiving CRT-D, risks of mortality (hazard ratio, 0.83; 95% confidence interval, 0.75–0.92), all-cause readmission (hazard ratio, 0.86; 95% confidence interval, 0.80–0.92), and heart failure readmission (hazard ratio, 0.68; 95% confidence interval, 0.62–0.76) were lower with CRT-D compared with ICD alone. There was no significant difference in the 90-day complication rate (hazard ratio, 0.88; 95% confidence interval, 0.60–1.29). We observed hospital-level variation in the use of CRT-D among patients with atrial fibrillation.

Conclusions—Among eligible patients with heart failure and atrial fibrillation, CRT-D was associated with lower risks of mortality, all-cause readmission, and heart failure readmission, as well as with a similar risk of complications compared with ICD alone. **(*Circ Heart Fail*. 2016;9:e002324. DOI: 10.1161/CIRCHEARTFAILURE.115.002324.)**

Key Words: atrial fibrillation ■ cardiac resynchronization therapy ■ heart failure ■ hospitalization ■ prevalence

Cardiac resynchronization therapy with defibrillator (CRT-D) improves survival and prevents hospitalizations in patients with symptomatic heart failure, reduced left ventricular ejection fraction, and prolonged QRS duration.[1–6] The prevalence of atrial fibrillation in this population is 25% to 50%, and many patients with concurrent heart failure and atrial fibrillation have reduced left ventricular ejection fraction with dyssynchrony. However, clinical practice guidelines designate CRT-D as a class IIa indication in patients with heart failure and atrial fibrillation who otherwise meet clinical criteria for CRT-D.[7,8]

See Clinical Perspective

It is unclear whether CRT-D is beneficial compared with an implantable cardioverter-defibrillator (ICD) alone.[9] Patients with atrial fibrillation are poorly represented in clinical trials of CRT-D, despite its common co-occurrence with heart failure. Randomized trials of CRT-D in heart failure have evaluated devices in only 272 patients with atrial fibrillation (3.6% of all patients).[10] Data from observational studies are also limited[11] but suggest that CRT-D is less beneficial in patients with atrial fibrillation.[9,12]

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From the Duke Clinical Research Institute (P.K., M.A.G., S.M.A.-K., J.P.P., L.H.C., A.F.H.) and Department of Medicine (P.K., S.M.A.-K., J.P.P., L.H.C., A.F.H.), Duke University School of Medicine, Durham, NC; Veterans Affairs Eastern Colorado Healthcare System, Denver, CO (P.D.V.); University of Colorado Anschutz Medical Campus, Aurora, CO (F.A.M.); and Veterans Affairs Palo Alto Health Care System, Palo Alto, CA and Stanford University School of Medicine, CA (M.P.T.).

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Correspondence to Adrian F. Hernandez, MD, MHS, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715. E-mail adrian.hernandez@duke.edu

We assessed current use of CRT-D and ICD alone in clinical practice and measured the comparative effectiveness of CRT-D among eligible patients with heart failure and atrial fibrillation.

Methods

Data Sources

We obtained clinical data from the National Cardiovascular Data Registry's ICD Registry. The registry is the official repository of ICD implantation data for Medicare beneficiaries since April 2006 and is used in >1400 hospitals in the United States.[13] Registry data include demographic characteristics, medical history, discharge medications, and clinical and procedural information.[14,15]

To analyze long-term follow-up data, we obtained Medicare inpatient claims and the corresponding denominator files from the US Centers for Medicare and Medicaid Services for all Medicare beneficiaries between January 1, 2006, and December 31, 2011. The denominator files contain beneficiary demographic characteristics, enrollment information, and death dates. The inpatient files contain hospital claims covered under Medicare Part A and include service dates and diagnosis and procedure codes. We linked records from the ICD Registry to the Medicare inpatient files using methods described previously.[16]

Study Cohort

We included fee-for-service Medicare beneficiaries aged ≥65 years who had a registry record for CRT-D or ICD implantation during a hospital stay between April 1, 2006, and December 31, 2009; had a medical history of heart failure and atrial fibrillation or atrial flutter documented in the registry; were admitted for the procedure; and were discharged alive to home. We required that the patients have a QRS duration of ≥120 ms and left ventricular ejection fraction of ≤35%, consistent with guidelines for CRT-D.[8,17] We excluded patients with previous epicardial lead implantation, previous placement of an ICD or pacemaker, implantation for secondary prevention, previous cardiac arrest, myocardial infarction in the previous 40 days, or coronary artery bypass graft surgery or percutaneous coronary intervention during the implantation hospitalization.

Treatments

The treatments of interest were CRT-D and receipt of an ICD alone as recorded in the ICD Registry.

Outcomes

The outcomes of interest were all-cause mortality, all-cause and heart failure readmission, and device-related complications. We identified deaths on the basis of death dates in the Medicare denominator files, and we identified readmissions and complications on the basis of Medicare inpatient claims. The follow-up period for the mortality and readmission outcomes was 3 years after discharge from the index hospitalization; the follow-up period for device-related complications was 90 days. All-cause readmission was based on Medicare inpatient claims, excluding transfers to another hospital and admissions for rehabilitation (*International Classification of Disease, Ninth Revision, Clinical Modification* [*ICD-9-CM*] diagnosis code V57.xx or Diagnostic-Related Group code 462 before October 1, 2007, or Diagnostic-Related Group code 945 or 946 after October 1, 2007). Heart failure readmission was based on a primary diagnosis of heart failure (*ICD-9-CM* code 428.x, 402.x1, 404.x1, or 404.x3). Complications included pneumothorax or hemothorax (*ICD-9-CM* codes 512.1, 511.8, or 511.89), cardiac tamponade or pericardiocentesis (*ICD-9-CM* code 420.x, 423.0, 423.3, or 423.9 or procedure codes 37.0 or 37.12), hematoma (*ICD-9-CM* code 998.1x), mechanical complications of ICD with system revision (*ICD-9-CM* code 996.04 or 996.01 combined with procedure code 37.75, 37.79, 37.97, 37.99, or 00.52), and infection (*ICD-9-CM* code 996.61).

Subgroups

We prespecified clinically important subgroups, including current warfarin use and intraventricular conduction delay type combined with QRS duration. We ascertained warfarin use based on discharge medications listed in the registry. We categorized intraventricular conduction delay and QRS duration into 4 subgroups addressed by guideline recommendations for device-based therapy: left bundle branch block (LBBB) and QRS duration of ≥150 ms; LBBB and QRS duration of 120 to 149 ms; no LBBB and QRS duration of ≥150 ms; and no LBBB and QRS duration of 120 to 149 ms.[18]

Patient and Hospital Characteristics

We obtained baseline patient and hospital characteristics from the registry. Data for demographic variables were complete, and the other variables had low rates of missingness (ie, <5% of records). We imputed values for missing continuous variables to the median. We imputed values for missing dichotomous variables to no and for missing multichotomous variables to the most frequent category.[19] We considered patient demographic characteristics, medical history, diagnostic data, vital signs and laboratory test results, year of procedure, hospital characteristics, and whether the physician had training in adult electrophysiology. We calculated the total hospital-level volume of ICD implantations based on the full registry from April 1, 2006, through December 31, 2009. We annualized hospital procedure volume by dividing the total count by the number of quarters the hospital participated in the registry multiplied by 4. We then assigned hospitals to quartiles based on their volume ranking among hospitals in the study cohort.

Statistical Analysis

We describe baseline characteristics of the study population using proportions for categorical variables and means with SDs or medians with 25th and 75th percentiles for continuous variables. We tested for differences between groups using χ^2 tests for categorical variables and Kruskal–Wallis tests for continuous variables. We assessed hospital-level variation in CRT-D use by calculating the rate of CRT-D use per hospital as the number of CRT-D implants divided by the total number of CRT-D and ICD devices in the all-comers cohort (ie, patients with any reason for admission). We describe hospital-level variation in CRT-D rates with medians, quartiles, and ranges. We describe hospital characteristics by quartiles of hospital-level CRT-D rates.

We report observed event rates by treatment group. For mortality, we used Kaplan–Meier methods to calculate event rates and log-rank tests to assess differences between groups. For the readmission end points, we used the cumulative incidence function, which accounts for the competing risk of mortality. We used Gray tests to assess differences in outcomes between groups. The censoring date was the earliest of the end of the ascertainment period (ie, 90 days or 3 years), the end of the period for which data were available (ie, December 31, 2011), or the date on which the patient's data were no longer available because the patient enrolled in a Medicare managed care plan. For outcomes other than death, we censored data at the time of death.

Because the study relied on observational data and CRT-D devices are more likely to be implanted in patients with more severe heart failure, there is the potential for bias in the treatment effect related to patient differences by treatment selection. Therefore, to assess differences in outcomes between the treatment groups, we used inverse probability-weighted estimates to adjust for the probability of a patient receiving the treatment conditional on observed covariates.[20] The inverse probability-weighted approach adjusts for confounding related to treatment selection, resulting in pseudorandom assignment of patients to either CRT-D or ICD. Using the baseline characteristics of the study population, we used a logistic regression model to estimate the probability of each patient receiving CRT-D. We then assigned a weight to each patient based on the inverse of the estimated probability of the treatment received. To assess the effectiveness of the propensity model to balance the treatment groups, we used standardized differences, weighted χ^2 tests for categorical variables, and weighted ANOVA for continuous variables to compare baseline

characteristics between the treatment groups after weighting.[21] We considered the baseline characteristics to be balanced if the standardized difference was <10%.

We used weighted Cox proportional hazards models to estimate associations between CRT-D and outcomes. We assessed differences in the effect of CRT-D subgroup by testing interactions between subgroup variables and CRT-D. For significant interactions, we calculated estimates of the association between CRT-D and the outcome within each subgroup. As a sensitivity analysis to test whether the propensity models adequately controlled for unmeasured confounding, we examined the association between CRT-D and readmission for hip fracture (primary ICD-9-CM diagnosis code 820.x), a noncardiovascular outcome related to overall health status. We report hazard ratios (HRs) and 95% confidence intervals (CIs) based on robust SEs to account for clustering of patients by hospital.

We used a significance level of 0.05 and 2-sided tests for all hypotheses. We used SAS version 9.3 (SAS Institute, Inc, Cary, NC) for all analyses. The institutional review board of the Duke University Health System approved the study.

Results

The study population included 8951 patients with heart failure and atrial fibrillation (Figure). Patients who received CRT-D were of similar age and were more likely to be women and to have nonischemic cardiomyopathy and had more severe heart failure based on New York Heart Association functional class III or IV symptoms, QRS duration of ≥150 ms, and LBBB morphology, compared with patients who received an ICD (Table 1). Physicians with adult electrophysiology training performed a majority of the device implantations and were more likely to implant a CRT-D device than an ICD. The hospital-level rate of CRT-D use ranged from 32% to 100% of total implants (25th–75th percentile, 69%–86%). Hospitals in the highest quartile of CRT-D use were more likely to be private/community hospitals, to be in rural regions, and to have fewer beds, compared with hospitals in the lowest quartile (Table I in the Data Supplement).

Rates of all-cause mortality and all-cause readmission within 3 years were similar between the treatment groups (Table 2). Rates of heart failure readmission were slightly lower in the CRT-D group. Complication rates within 90 days were similar between the groups.

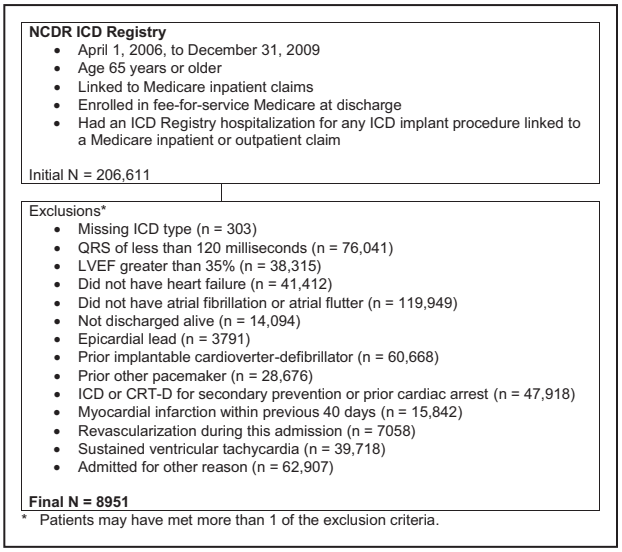

Figure. Derivation of the study cohort. CRT-D indicates cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; and NCDR, National Cardiovascular Data Registry.

After weighting by the inverse probability of treatment, the baseline characteristics were similar between the treatment groups based on a standardized difference of <10% (Tables II and III in the Data Supplement). CRT-D was associated with lower risk of all-cause mortality (HR, 0.83; 95% CI, 0.75–0.92; P<0.001), all-cause readmission (HR, 0.86; 95% CI, 0.80–0.92; P<0.001), and heart failure readmission (HR, 0.68; 95% CI, 0.62–0.76; P<0.001) within 3 years but was not associated with 90-day complications (HR, 0.88; 95% CI, 0.60–1.29; P=0.51), compared with receipt of an ICD (Table 3). We compared results from traditional multivariable-adjusted Cox models to results from multivariable-adjusted Cox models stratified by New York Heart Association class. There were no differences in CRT-D associations when we explicitly controlled for New York Heart Association class in the stratified Cox models (Table IV in the Data Supplement). Furthermore, these associations were similar to the inverse probability-weighted estimates. Results were similar in the secondary cohort of patients who were admitted for other reasons (Table V in the Data Supplement). In the sensitivity analysis to test for possible residual confounding, we observed no association between CRT-D and hip fracture at 3 years compared with ICD (data not shown).

In subgroup analyses, the association between CRT-D and the lower hazard of 3-year mortality and 90-day complications was greater among patients who were not treated with warfarin (P=0.03 and P=0.004 for the interaction, respectively; Table VI in the Data Supplement). The association between CRT-D and a lower hazard of heart failure readmission was greater among patients with LBBB or longer QRS duration (P<0.001 for the interaction; Table 4). In the secondary cohort of patients who were admitted for reasons other than the device implantation, the association between CRT-D and a lower hazard of mortality was only significant among patients with LBBB and a QRS duration of ≥150 ms (P<0.001).

Discussion

Ours is among the largest studies of the effectiveness of CRT-D in patients with atrial fibrillation. Among older patients with heart failure and atrial fibrillation, CRT-D was associated with lower mortality, all-cause readmission, and heart failure readmission compared with ICD implantation. Also, the association between CRT-D and a lower hazard of heart failure readmission was greater among patients with LBBB or longer QRS duration. Moreover, there was no association between CRT-D and 90-day complications compared with ICD implantation.

CRT-D has a greater mortality benefit than ICDs among patients with heart failure, significant left ventricular dysfunction, and prolonged QRS duration.[4,22] However, the effectiveness of CRT-D in patients with both heart failure and atrial fibrillation remains controversial. Small observational studies have suggested that atrial fibrillation minimizes the benefits of CRT-D because of reduced biventricular pacing or lack of atrioventricular optimization.[23] Clinical trials of CRT-D have often excluded patients with atrial fibrillation.[4] Our analysis of CRT-D versus

Table 1. Baseline Characteristics of the Study Population

Characteristic	ICD Alone (n=2481)	CRT-D (n=6470)	Standardized Difference	*P* Value
Age at implantation, mean (SD), y	75.4 (6.0)	75.8 (6.0)	6.8	0.001
Men, n (%)	1996 (80)	4886 (75)	11.9	<0.001
Race, n (%)			2.0	0.70
Black	97 (4)	268 (4)		
White	2330 (94)	6046 (93)		
Other/unknown	54 (2)	156 (2)		
Medical history, n (%)				
Abnormal sinus node function	1176 (47)	3237 (50)	5.3	0.03
Cerebrovascular disease	420 (17)	1113 (17)	0.7	0.76
Chronic lung disease	535 (22)	1583 (25	6.9	0.004
Diabetes mellitus	851 (34)	2380 (37)	5.2	0.03
Hypertension	1929 (78)	5131 (79)	3.8	0.11
Ischemic heart disease	1826 (74)	4204 (65)	18.8	<0.001
Nonischemic dilated cardiomyopathy	730 (29)	2402 (37)	16.4	<0.001
Nonsustained ventricular tachycardia	476 (19)	1020 (16)	9.0	<0.001
Coronary artery bypass graft surgery	1205 (49)	2752 (43)	12.1	<0.001
Myocardial infarction	1419 (57)	3110 (48)	18.4	<0.001
Percutaneous coronary intervention	731 (30)	1849 (29)	2.0	0.41
Valvular surgery	320 (13)	868 (13)	1.5	0.52
Renal failure, dialysis	72 (3)	192 (3)	0.4	0.87
Diagnostic and ICD characteristics				
New York Heart Association class, n (%)			120.0	<0.001
I	114 (5)	41 (1)		
II	1352 (55)	625 (10)		
III	974 (39)	5506 (85)		
IV	41 (2)	298 (5)		
Ejection fraction, mean (SD), %	25.6 (6)	24.7 (6)	15.7	<0.001
Severely impaired (≤25%), n (%)	1348 (54)	3935 (61)	13.2	<0.001
QRS duration, mean (SD), ms	144 (22)	151 (21)	35.3	<0.001
QRS duration ≥150 ms	884 (36)	3286 (51)	31.0	<0.001
Intraventricular conduction, n (%)			58.6	<0.001
Normal	483 (20)	443 (7)		
Left bundle branch block	864 (35)	3919 (61)		
Right bundle branch block	551 (22)	1019 (16)		
Intraventricular conduction delay	477 (19)	776 (12)		
Other abnormal conduction	106 (4)	313 (5)		
Atrioventricular conduction, n (%)			14.2	<0.001
Normal	1867 (75)	4613 (71)		
First-degree heart block	481 (19)	1350 (21)		
Second- or third-degree heart block (not paced)	88 (4)	247 (4)		
Paced (any)	45 (2)	260 (4)		

(*Continued*)

Table 1. Continued

Characteristic	ICD Alone (n=2481)	CRT-D (n=6470)	Standardized Difference	*P* Value
Laboratory test results				
Systolic blood pressure, mean (SD), mm Hg	133 (22)	132 (22)	7.3	0.001
Systolic blood pressure, n (%)			6.0	0.04
<110 mm Hg	303 (12)	915 (14)		
110–150 mm Hg	1686 (68)	4349 (67)		
>150 mm Hg	492 (20)	1206 (19)		
Serum sodium, mean (SD), mEq/L	139 (3)	138 (3)	4.5	0.04
Serum sodium, n (%)			6.1	0.04
<135 mEq/L	181 (7)	570 (9)		
135–145 mEq/L	2273 (92)	5813 (90)		
>145 mEq/L	27 (1)	87 (1)		
Serum creatinine, mean (SD), mg/dL	1.4 (1)	1.4 (1)	7.3	<0.001
Serum creatinine, n (%)			8.2	0.003
<1.5 mg/dL	1719 (69)	4250 (66)		
1.5–2.0 mg/dL	566 (23)	1601 (25)		
>2.0 mg/dL	196 (8)	619 (10)		
Blood urea nitrogen, mean (SD), mg/dL	26.2 (13)	28.1 (15)	13.5	<0.001
Blood urea nitrogen, n (%)			10.9	<0.001
<20 mg/dL	829 (33)	1852 (29)		
20–49 mg/dL	1496 (60)	4126 (64)		
>50 mg/dL	156 (6)	492 (8)		
Discharge medications, n (%)				
ACE inhibitor or ARB	1927 (78)	4933 (76)	3.4	0.15
Amiodarone	440 (18)	1399 (22)	9.8	<0.001
β-Blocker	2084 (84)	5546 (86)	4.8	0.04
Calcium-channel blocker	100 (4)	197 (3)	5.3	0.02
Digoxin	810 (33)	2354 (36)	7.9	<0.001
Diuretic	1840 (74)	5196 (80)	14.7	<0.001
Dofetilide	14 (1)	50 (1)	2.6	0.29
Statin	1699 (69)	4061 (63)	12.1	<0.001
Warfarin	1535 (62)	4062 (63)	1.9	0.43
Year of procedure, n (%)			12.8	<0.001
2006	563 (23)	1258 (19)		
2007	736 (30)	1730 (27)		
2008	607 (25)	1717 (27)		
2009	575 (23)	1765 (27)		
Physician had adult electrophysiology training	1789 (72)	5159 (80)	17.9	<0.001
Hospital characteristics				
Annualized ICD volume, median (25th–75th percentile)	168 (89–305)	186 (103–305)	6.1	<0.001
Type			2.3	0.61
Academic	300 (12)	752 (12)		
Government	48 (2.0)	110 (2)		

(*Continued*)

Table 1. Continued

Characteristic	ICD Alone (n=2481)	CRT-D (n=6470)	Standardized Difference	*P* Value
Private/community	2133 (86)	5608 (87)		
Geographic location			2.0	0.70
Rural	278 (11)	685 (11)		
Urban	1475 (60)	3871 (60)		
Suburban	728 (29)	1914 (30)		
Patient beds, median (25th–75th percentile)	428 (291–583)	426 (294–585)	2.1	0.64
In-hospital complication occurred	60 (2)	228 (4)	6.5	0.008

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CRT-D, cardiac resynchronization therapy with defibrillator; and ICD, implantable cardioverter-defibrillator.

ICD in clinical practice helps bridge this knowledge gap. More recent trials examining CRT-D in patients with less severe heart failure and in specific populations included patients with atrial arrhythmias, but extrapolating data from these studies can be challenging given their narrow inclusion criteria and idealized settings. In a substudy of the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial among patients with atrial fibrillation and heart failure, CRT-D was associated with no difference in the primary outcome of death or heart failure hospitalization compared with ICD alone, but there was a trend toward fewer heart failure hospitalizations among patients receiving CRT-D.[11] The Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) substudy found that the benefit of CRT-D in patients with LBBB was not significantly different among patients with intermittent atrial tachyarrhythmia compared with those without, and the percentage of patients with biventricular pacing was similar in both groups.[23]

Previous observational studies suggest that CRT-D attenuates the frequency or duration of atrial fibrillation in patients with heart failure.[24] These studies suggest that atrial fibrillation burden declines in the first 3 to 6 months after CRT-D implantation[25,26] and resolves altogether in some patients.[27] Patients may also experience better outcomes with a high degree of biventricular pacing or atrioventricular junction ablation.[28–30] A meta-analysis of 23 observational studies found that atrial fibrillation was associated with a higher risk of nonresponse and all-cause mortality, but only a quarter of the patients had atrial fibrillation.[9] In a previous analysis, we found that, among eligible patients, CRT-D was associated with lower mortality and readmission rates compared with ICD, and a subgroup analysis suggested that CRT-D may be associated with lower mortality and readmission in patients with and without atrial fibrillation.[22] However, this subgroup analysis was small and limited by the matching method.

Table 2. Cumulative Incidence of Mortality, Readmission, and Complications After Discharge From Hospitalization for Defibrillator Implantation

Outcome	Overall (n=8951)	ICD Alone (n=2481)	CRT-D (n=6470)	*P* Value
Mortality				
1 y	990 (11.3)	252 (10.4)	738 (11.7)	0.10
3 y	2637 (32.4)	744 (33.0)	1893 (32.2)	0.68
All-cause readmission				
1 y	4333 (49.2)	1211 (49.6)	3122 (49.0)	0.82
3 y	6449 (75.8)	1788 (75.6)	4661 (75.9)	0.84
Heart failure readmission				
1 y	1716 (19.5)	492 (20.2)	1224 (19.2)	0.31
3 y	2878 (34.2)	844 (36.2)	2034 (33.4)	0.02
Complications				
90 d	263 (2.9)	67 (2.7)	196 (3.0)	0.41

Values are expressed as number (cumulative incidence). CRT-D indicates cardiac resynchronization therapy with defibrillator; and ICD, implantable cardioverter-defibrillator.

Among patients with heart failure and atrial fibrillation who were eligible for CRT-D, 72% received CRT-D and 28% received an ICD. This difference is likely related to multiple factors, including provider preference, level of training, specialty, difficulty placing the coronary sinus lead, availability of the procedure, patient preference, and the presence of renal disease. A previous analysis of data from the ICD Registry found that nonelectrophysiologists implanted 29% of ICDs, and among patients eligible for CRT-D, nonelectrophysiologists were less likely to implant a CRT-D and had higher associated risk of procedural complications with CRT-D compared with ICD implantation.[31] Our study of more recent data provides similar evidence in patients who were eligible for CRT-D but also had atrial fibrillation.

CRT-D was associated with the largest risk difference in patients with LBBB with QRS duration of ≥150 ms. There was no association in patients who had no LBBB and QRS duration of 120 to 149 ms. Our observations support current guidelines that designate patients with both LBBB and QRS duration of ≥150 ms as having the strongest indication for CRT-D compared with ICD (ie, class I, level of evidence A), and patients with LBBB and QRS duration of 120 to 149 ms and no LBBB and QRS duration of ≥150 ms as having a class IIa indication.[8] This observation is consistent with recent findings that patients with LBBB and QRS duration of ≥150 ms have lower risk of all-cause mortality and readmission.[32]

Finally, we observed no difference in 90-day complications. Previous analyses suggested that CRT-D is associated

Table 3. Associations Between Cardiac Resynchronization Therapy With Defibrillator and Outcomes Compared With Implantable Cardioverter-Defibrillator Alone*

Outcome	Unadjusted HR (95% CI)	Unadjusted *P* Value	Weighted HR* (95% CI)	Weighted *P* Value
3-yr mortality	0.98 (0.90–1.07)	0.67	0.83 (0.75–0.92)	<0.001
3-y all-cause readmission	0.99 (0.94–1.05)	0.85	0.86 (0.80–0.92)	<0.001
3-y heart failure readmission	0.92 (0.84–0.99)	0.04	0.68 (0.62–0.76)	<0.001
90-d complications	1.12 (0.84–1.50)	0.43	0.88 (0.60–1.29)	0.51

CI indicates confidence interval; and HR, hazard ratio.
*Inverse probability-weighted estimates.

with higher 3-year device-related infection and mechanical device complications.[22] However, in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial substudy of patients with atrial fibrillation, there was no significant difference in perioperative complications between CRT-D and ICD.[11] One potential reason for this finding is that more electrophysiologists implant devices, and both electrophysiologists and nonelectrophysiologists have gained experience over time, narrowing the gap in complication rates. We also found greater associations between CRT-D and lower hazard of 3-year mortality and statistically significant lower hazard of 90-day complications among patients not treated with warfarin. Because all patients with heart failure and atrial fibrillation have a class I indication for oral anticoagulation, patients who are not candidates for warfarin are likely sicker and have greater absolute benefit from CRT-D.

Our study has limitations. First, despite our use of propensity scores and inverse probability weighting, observed associations between treatment and outcomes may be influenced by residual confounding because patients were not randomly assigned to treatment. Second, because the study population consisted of fee-for-service Medicare beneficiaries aged ≥65 years, the results may not be generalizable to younger populations. However, the analysis provides important information about this population because a majority of patients with heart failure are older and are under-represented in clinical trials. Third, the ICD Registry has limited information about the burden of atrial fibrillation and does not have information on the type of atrial fibrillation (ie, paroxysmal, persistent, or permanent). It does not capture information about rate control, devices programming, biventricular pacing, or atrioventricular nodal ablation. Finally, we could not assess quality of life or functional status as outcomes.

Conclusions

This large observational comparative effectiveness study of CRT-D among patients with both heart failure and atrial fibrillation provides an important perspective on the associated outcomes of CRT-D as currently used in clinical practice. We observed marked hospital-level variation in the use of CRT-D among patients with atrial fibrillation. CRT-D was associated with lower mortality, all-cause readmission, and heart failure readmission but no difference in 90-day complications, compared with ICD alone.

Table 4. Results of the Inverse Probability-Weighted Model of Associations Between Cardiac Resynchronization Therapy With Defibrillator and Outcomes by Left Bundle Branch Block and QRS Duration

Outcome	Unadjusted HR (95% CI)	Unadjusted *P* Value	Weighted HR (95% CI)	Weighted *P* Value
Study cohort*				
3-y heart failure readmission				
LBBB/QRS ≥150 ms	0.72 (0.60–0.87)	<0.001	0.50 (0.41–0.61)	<0.001
LBBB/QRS 120–149 ms	0.81 (0.68–0.97)	0.02	0.60 (0.48–0.75)	<0.001
No LBBB/QRS ≥150 ms	0.93 (0.77–1.13)	0.47	0.71 (0.56–0.91)	0.005
No LBBB/QRS 120–149 ms	1.29 (1.13–1.47)	<0.001	1.03 (0.87–1.21)	0.74
Secondary cohort of patients admitted for other reasons†				
3-y mortality				
LBBB/QRS ≥150 ms	0.62 (0.48–0.80)	<0.001	0.59 (0.43–0.81)	<0.001
LBBB/QRS 120–149 ms	0.79 (0.63–1.01)	0.06	0.82 (0.62–1.09)	0.16
No LBBB/QRS ≥150 ms	0.97 (0.76–1.24)	0.82	0.98 (0.74–1.30)	0.90
No LBBB/QRS 120–149 ms	1.17 (0.98–1.38)	0.08	1.18 (0.97–1.42)	0.09

CI indicates confidence interval; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; and LBBB, left bundle branch block.
*CRT-D–LBBB/QRS interactions were statistically insignificant for 3-y mortality, 3-y all-cause readmission, and 90-d complications.
†CRT-D–warfarin interactions were statistically insignificant for all outcomes in the secondary cohort. CRT-D–LBBB/QRS interactions were statistically insignificant for 3-y all-cause readmission, 3-y heart failure readmission, and 90-d complications in the secondary cohort.

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CLINICAL PERSPECTIVE

Patients with atrial fibrillation are poorly represented in clinical trials of cardiac resynchronization therapy with defibrillator (CRT-D), despite the common co-occurrence of atrial fibrillation and heart failure. It is unclear whether CRT-D is beneficial compared with an implantable cardioverter-defibrillator alone. In this large, retrospective observational study of data from the National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry and Medicare administrative claims files, we assessed current use of CRT-D and implantable cardioverter-defibrillator alone in clinical practice and measured the comparative effectiveness of CRT-D among eligible patients with heart failure and atrial fibrillation. We observed marked hospital-level variation in the use of CRT-D. CRT-D was associated with lower mortality, all-cause readmission, and heart failure readmission but no difference in 90-day complications compared with implantable cardioverter-defibrillator alone.

Circulation
Heart Failure

Comparative Effectiveness of Cardiac Resynchronization Therapy Among Patients With Heart Failure and Atrial Fibrillation: Findings From the National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry

Prateeti Khazanie, Melissa A. Greiner, Sana M. Al-Khatib, Jonathan P. Piccini, Mintu P. Turakhia, Paul D. Varosy, Frederick A. Masoudi, Lesley H. Curtis and Adrian F. Hernandez for the National Cardiovascular Data Registry

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Characteristics of Hospitals Cohort With More than 25 Implants in the All-Comers by Quartile of CRT-D Use (N = 151)

Supplemental Table 2. Results of the Propensity Model for CRT-D Use

Supplemental Table 3. Baseline Characteristics of the Study Population Weighted by the Inverse Probability of Treatment

Supplemental Table 4. Associations Between CRT-D and Outcomes Compared With ICD Alone Using Traditional Multivariable Models

Supplemental Table 5. Results of the Inverse Probability-Weighted Model in the Secondary Cohort of Patients Admitted for Other Reasons

Supplemental Table 6. Results of the Inverse Probability-Weighted Model of the Association Between CRT-D and Outcomes by Warfarin Status

Supplemental Table 1. Characteristics of Hospitals With More Than 25 Implants in the All-Comers Cohort by Quartile of CRT-D Use (N = 151)*

Characteristic	Quartile 1 (32%-67%)	Quartile 2 (68%-78%)	Quartile 3 (79%-86%)	Quartile 4 (87%-100%)
No. of hospitals	38	40	38	38
Annualized ICD volume, median (25th-75th percentile)	318 (224-402)	306 (238-408)	261 (176-346)	278 (225-364)
Hospital type, No. (%)				
Private/community	29 (76)	33 (83)	32 (84)	33 (87)
Government	1 (2)	0	1 (3)	0
Academic	8 (21)	7 (18)	5 (13)	5 (13)
Geographic setting, No. (%)				
Rural	1 (3)	3 (8)	4 (11)	6 (16)
Urban	27 (71)	23 (58)	23 (61)	24 (63)
Suburban	10 (26)	14 (35)	11 (29)	8 (21)
US geographic region, No. (%)				
Midwest	12 (32)	16 (40)	9 (24)	6 (16)
Northeast	7 (18)	8 (20)	9 (24)	10 (26)
South	18 (47)	15 (38)	17 (45)	19 (50)
West	1 (3)	1 (3)	3 (8)	3 (8)
Beds, median (IQR)	518 (412-797)	603 (446-839)	506 (414-700)	416 (283-600)

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; IQR, interquartile range.

* The overall median rate of CRT-D use was 77.8% (25th-75th percentile, 68.6%-86.0%; range, 32.4%-100.0%).

Supplemental Table 2. Results of the Propensity Model for CRT-D Use

Variable	Odds Ratio (95% CI)	*P* Value
Age at ICD implantation per 5 years	1.03 (0.98-1.08)	0.21
Male	1.02 (0.88-1.17)	0.83
Race		
Black	0.83 (0.62-1.10)	0.20
White	1.00 [Reference]	
Other/unknown	1.17 (0.81-1.70)	0.40
Medical history		
Abnormal sinus node function	1.05 (0.93-1.17)	0.44
Cerebrovascular disease	0.98 (0.85-1.14)	0.84
Chronic lung disease	1.06 (0.93-1.22)	0.36
Diabetes mellitus	1.06 (0.94-1.20)	0.32
Hypertension	1.10 (0.95-1.26)	0.20
Ischemic heart disease	0.80 (0.67-0.96)	0.02
Nonsustained ventricular tachycardia	0.78 (0.67-0.90)	< 0.001
Prior coronary artery bypass graft surgery	0.99 (0.86-1.14)	0.93
Prior myocardial infarction	0.81 (0.70-0.93)	0.004
Prior percutaneous coronary intervention	1.10 (0.96-1.26)	0.17
Prior valvular surgery	0.96 (0.81-1.14)	0.62
Renal failure, dialysis	0.87 (0.61-1.24)	0.43
NYHA class		
I	0.07 (0.05-0.10)	< 0.001
II	0.09 (0.08-0.10)	< 0.001
III	1.00 [Reference]	
IV	1.31 (0.92-1.85)	0.13
Severely impaired ejection fraction (≤ 25%)	1.15 (1.03-1.29)	0.02
QRS ≥ 150 ms	1.36 (1.20-1.53)	< 0.001
Intraventricular conduction		
Normal	1.00 [Reference]	
LBBB	3.68 (3.08-4.41)	< 0.001
RBBB	1.73 (1.42-2.12)	< 0.001
Intraventricular conduction delay	1.72 (1.40-2.11)	< 0.001
Other abnormal conduction	2.22 (1.59-3.10)	< 0.001
Atrioventricular conduction		
Normal	1.00 [Reference]	
First-degree heart block only	1.05 (0.91-1.22)	0.46
Second- or third-degree heart block, not paced	1.23 (0.91-1.65)	0.18
Paced, any	1.99 (1.33-2.99)	< 0.001
Systolic blood pressure		
< 110 mmHg	1.04 (0.88-1.24)	0.63
110-150 mm Hg	1.00 [Reference]	
> 150 mmHg	1.02 (0.88-1.18)	0.82
Serum sodium		
< 135 mEq/L	1.09 (0.89-1.35)	0.41
135-145 mEq/L	1.00 [Reference]	
> 145 mEq/L	1.10 (0.66-1.84)	0.72
Serum creatinine		
< 1.5 mg/dL	1.00 [Reference]	
1.5-2.0 mg/dL	1.01 (0.87-1.17)	0.88
> 2.0 mg/dL	1.10 (0.86-1.40)	0.46

Variable	Odds Ratio (95% CI)	*P* Value
Blood urea nitrogen		
< 20 mg/dL	0.90 (0.79-1.03)	0.11
20-49 mg/dL	1.00 [Reference]	
≥ 50 mg/dL	0.80 (0.62-1.03)	0.09
Year of procedure	1.14 (1.09-1.20)	< 0.001
Hospital type		
Academic	0.93 (0.78-1.11)	0.41
Government	0.88 (0.58-1.35)	0.56
Private/community	1.00 [Reference]	
Annualized ICD volume		
Quartile 1 (< 43)	1.00 [Reference]	
Quartile 2 (43-85)	1.82 (1.40-2.38)	< 0.001
Quartile 3 (86-153)	1.73 (1.35-2.21)	< 0.001
Quartile 4 (> 153)	1.94 (1.54-2.45)	< 0.001
Physician training in adult electrophysiology	1.53 (1.34-1.74)	< 0.001

Supplemental Table 3. Baseline Characteristics of the Study Population Weighted by the Inverse Probability of Treatment

Characteristic	ICD Alone (n = 2481)	CRT-D (n = 6470)	Standardized Difference, %	*P* Value
Age at implantation, mean (SD), y	75.9 (5.9)	75.8 (6.0)	1.2	0.61
Male, No. (%)	1996 (77)	4886 (77)	0.2	0.92
Race			2.5	0.56
Black	97 (5)	268 (5)		
White	2330 (92)	6046 (93)		
Other/unknown	54 (3)	156 (2)		
Medical history, No. (%)				
Abnormal sinus node function	1176 (51)	3237 (50)	1.8	0.43
Cerebrovascular disease	420 (18)	1113 (17)	0.5	0.82
Chronic lung disease	535 (23)	1583 (24)	2.6	0.27
Diabetes mellitus	851 (37)	2380 (36)	1.0	0.67
Hypertension	1929 (79)	5131 (79)	0.2	0.94
Ischemic heart disease	1826 (68)	4204 (67)	0.5	0.83
Nonsustained ventricular tachycardia	476 (17)	1020 (17)	0.2	0.92
Prior coronary artery bypass graft surgery	1205 (44)	2752 (44)	0.6	0.81
Prior myocardial infarction	1419 (50)	3110 (50)	0.5	0.84
Prior percutaneous coronary intervention	731 (29)	1849 (29)	0.3	0.89
Prior valvular surgery	320 (13)	868 (13)	0.1	0.97
Renal failure, dialysis	72 (4)	192 (3)	2.7	0.25
NYHA class, No. (%)			1.4	0.95
I	114 (2)	41 (2)		
II	1352 (22)	625 (22)		
III	974 (73)	5506 (72)		
IV	41 (4)	298 (4)		
Ejection fraction, mean (SD), %	24.8 (6)	24.9 (6)	0.8	0.75
Severely impaired (≤ 25%), No. (%)	1348 (60)	3935 (59)	2.4	0.32
QRS duration, mean (SD), ms	148.8 (23)	149.9 (21)	5.0	0.03
QRS duration ≥ 150 ms, No. (%)	884 (47)	3286 (47)	0.2	0.94
Intraventricular conduction, No. (%)			1.1	0.99
Normal	483 (10)	443 (10)		
LBBB	864 (54)	3919 (54)		
RBBB	551 (18)	1019 (18)		
Intraventricular conduction delay	477 (14)	776 (14)		
Other abnormal conduction	106 (5)	313 (5)		
Atrioventricular conduction, No. (%)			4.1	0.39

Characteristic	ICD Alone (n = 2481)	CRT-D (n = 6470)	Standardized Difference, %	*P* Value
Normal	1867 (73)	4613 (73)		
First-degree heart block only	481 (19)	1350 (20)		
Second- or third-degree heart block, not paced	88 (4)	247 (4)		
Paced, any	45 (4)	260 (3)		
Systolic blood pressure, mean (SD), mm Hg	132 (22)	132.3 (22)	0.8	0.73
Systolic blood pressure, No. (%)			4.6	0.15
< 110 mm Hg	303 (15)	915 (14)		
110-150 mm Hg	1686 (68)	4349 (67)		
> 150 mm Hg	492 (17)	1206 (19)		
Serum sodium, mean (SD), mEq/L	138.8 (4)	138.9 (3)	0.7	0.76
Serum sodium, No. (%)			1.9	0.71
< 135 mEq/L	181 (9)	570 (8)		
135-145 mEq/L	2273 (90)	5813 (90)		
> 145 mEq/L	27 (2)	87 (1)		
Serum creatinine, mean (SD), mg/dL	1 (1)	1 (1)	1.2	0.63
Serum creatinine, No. (%)			1.5	0.82
< 1.5 mg/dL	1719 (66)	4250 (66)		
1.5-2.0 mg/dL	566 (24)	1601 (24)		
> 2.0 mg/dL	196 (10)	619 (9)		
Blood urea nitrogen, mean (SD), mg/dL	27 (14)	28 (14)	2.7	0.25
Blood urea nitrogen, No. (%)			1.1	0.90
< 20 mg/dL	829 (30)	1852 (30)		
20-49 mg/dL	1496 (63)	4126 (63)		
≥ 50 mg/dL	156 (7)	492 (7)		
Year of procedure, No. (%)			4.1	0.40
2006	563 (20)	1258 (20)	1.6	
2007	736 (29)	1730 (27)	4.0	
2008	607 (25)	1717 (26)	0.9	
2009	575 (26)	1765 (26)	1.7	
Physician training in adult electrophysiology, No. (%)	1789 (771)	5159 (77)	0.9	0.71
Annualized hospital ICD volume, median (IQR)	181 (99-307)	178 (97-307)	1.6	0.50
Hospital type, No. (%)			4.0	0.27
Academic	300 (12)	752 (12)		
Government	48 (1)	110 (2)		
Private/community	2133 (87)	5608 (87)		

Supplemental Table 4. Results of the Inverse Probability-Weighted Model in the Secondary Cohort of Patients Admitted for Other Reasons

Outcome	Unadjusted HR (95% CI)	Unadjusted *P* Value	Weighted HR (95% CI)	Weighted *P* Value
3-year mortality	0.87 (0.78-0.97)	.01	0.86 (0.75-0.99)	0.03
3-year all-cause readmission	0.85 (0.78-0.91)	< .001	0.82 (0.75-0.91)	< 0.001
3-year heart failure readmission	0.87 (0.79-0.96)	.005	0.85 (0.74-0.97)	0.01
90-day complications	0.97 (0.67-1.41)	.87	0.80 (0.51-1.26)	0.34

Abbreviation: HR, hazard ratio.

Supplemental Table 5. Associations Between CRT-D and Outcomes Compared With ICD Alone Using Traditional Multivariable Models

Outcome	Multivariable-Adjusted HR (95% CI)	Multivariable-Adjusted *P* Value	NYHA Stratified (95% CI)	NYHA Stratified *P* Value
3-year mortality	0.84 (0.76-0.93)	< .001	0.84 (0.76-0.93)	< .001
3-year all-cause readmission	0.87 (0.82-0.93)	< .001	0.87 (0.82-0.94)	< .001
3-year heart failure readmission	0.76 (0.69-0.84)	< .001	0.76 (0.69-0.84)	< .001
90-day complications	0.92 (0.65-1.29)	.61	0.92 (0.65-1.29)	.61

Supplemental Table 6. Results of the Inverse Probability-Weighted Model of the Association Between CRT-D and Outcomes by Warfarin Status

Outcome*	Unadjusted HR (95% CI)	Unadjusted *P* Value	Weighted HR (95% CI)	Weighted *P* Value
3-year mortality				
Warfarin	1.06 (0.95-1.18)	0.28	0.92 (0.80-1.05)	0.22
No warfarin	0.87 (0.76-0.99)	0.04	0.72 (0.60-0.85)	< 0.001
90-day complications				
Warfarin	1.23 (0.85-1.79)	0.27	1.51 (0.91-2.52)	0.11
No Warfarin	1.00 (0.65-1.52)	0.99	0.55 (0.33-0.91)	0.02

Abbreviation: HR, hazard ratio.

* The CRT-D–warfarin interactions were statistically insignificant for 3-year all-cause readmission and 3-year heart failure readmission.