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Comparative Effectiveness of Cardiac Resynchronization Therapy in Combination With Implantable Defibrillator in Patients With Heart Failure and Wide QRS Duration

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Abstract

Several clinical trials have established that cardiac resynchronization therapy in combination with an implantable cardioverter-defibrillator improves survival and alleviates heart failure symptoms in appropriately selected patients. Recent guidelines have expanded the indications to include patients with less severe heart failure. The aim of this study was to examine the extent to which cardiac resynchronization therapy in combination with an implantable cardioverter-defibrillator improves survival and reduces risk for heart failure hospitalization in United States Medicare patients who met class I or class IIa recommendations. Propensity score methods were used to assess survival and rehospitalization outcomes in Medicare patients. Among patients who met class I recommendations, those with combined cardiac resynchronization therapy had significantly lower risk for death (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.77 to 0.88, $p < 0.0001$) and lower risk for rehospitalization (HR 0.88, 95% CI 0.83 to 0.94, $p < 0.0001$). Among patients who met class IIa recommendations, the relative hazard of death for patients with combined cardiac resynchronization therapy was lower (HR 0.90, 95% CI 0.85 to 0.96, $p = 0.0015$), but there was no significant difference in the risk for rehospitalization for heart failure (HR 1.03, 95% CI 0.97 to 1.10, $p = 0.2600$). In conclusion, cardiac resynchronization therapy in combination with an implantable cardioverter-defibrillator resulted in improved survival among Medicare patients meeting class I criteria and most patients meeting class IIa criteria as outlined in the current guidelines for device-based therapy in heart failure, although the effect sizes were lower than those demonstrated in recent trials.

Recent changes in guidelines for the implantation of cardiac resynchronization therapy (CRT) defibrillators (CRT-D) have heralded a paradigm shift in patient selection criteria for CRT-D.¹ Although CRT had previously been targeted to patients in New York Heart

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Supplementary Data

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Association (NYHA) classes III and IV only in previous guidelines, many patients in NYHA class II now have the strongest indication (class I) for CRT-D. In addition, patients with intermediate QRS durations (120 to 149 ms) were now given a downgraded but acceptable indication (class IIa), and some patients with previous indications no longer had indications at all in the present guidelines. Although these guideline changes were supported by clinical trials, we currently do not have high-quality published data in a large population of real-world patients in clinical practice regarding the long-term outcomes of patients implanted on the basis of the strength of current guideline-based indications. The present study fills this knowledge gap by examining long-term outcomes among Medicare patients with CRT-D implants compared with those of a propensity-matched cohort receiving standard implantable cardioverter-defibrillators (ICDs).

Methods

Beginning in 2005, the Centers for Medicare and Medicaid Services required hospitals to submit patient-level data to an ICD registry as part of policy changes that provided Medicare coverage of the costs associated with implantation of the devices. Medicare beneficiaries represent nearly the entire population of older patients in the United States with primary prevention ICDs. Medicare registry records for all patients who underwent ICD implantation occurring from January 2005 to April 2006 were obtained for this study.

Medicare hospital claims files, program eligibility records, and dates of death were obtained for patients with records in the ICD registry, for the period from January 2004 through June 2010. Registry records were matched to Medicare eligibility and utilization data using patients' Social Security numbers by the Centers for Medicare and Medicaid Services.² Medicare hospital claims data included the dates of hospital admission and International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes that identified the primary cause of hospitalization and concurrent secondary conditions. Dates of death were obtained for deceased patients from the Medicare program eligibility file records.

Subpopulations of Medicare patients with records in the ICD registry were defined for patients meeting class I or class IIa recommendations for CRT for patients in sinus rhythm on the basis of the American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society 2012 device-based therapy guidelines that summarize the available evidence for therapeutic efficacy.¹ Patients meeting class I criteria for CRT included those with left ventricular ejection fractions (LVEFs) $\geq 35\%$; those in NYHA class II, III, or IV; and those with left bundle branch block with QRS durations ≥ 150 ms. Class IIa criteria identify patients for whom it is reasonable to perform the procedure. Patients meeting class IIa criteria for CRT included those with LVEFs $\geq 35\%$; those in NYHA class II, III, or IV; and those with either left bundle branch block with QRS duration 120 to 149 ms or without left bundle branch block with QRS duration ≥ 150 ms. We did not include patients meeting the class IIa criteria of 40% right ventricular pacing or atrial fibrillation with atrioventricular node ablation or adequate pharmacologic rate control, because neither the percentage of ventricular pacing or adequacy of rate control could be assessed using the data available from the ICD registry.

Patients were followed for the occurrence of death from any cause and for the first occurrence of rehospitalization caused by heart failure (HF), for a minimum of 50 months and for up to 66 months, depending on the date of ICD implantation. The first occurrence of HF hospitalization was identified as the first inpatient hospital admission after ICD implantation with a primary International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code of 428.0 to 428.9 (congestive HF). The ICD registry uses Internet-based data collection that limits the potential for missing values in reported data elements. Each of the categorical and continuous patient characteristics included in the analysis had known values.

Multivariate logistic regression was used to estimate the probability of receiving CRT-D among all patients included in the 2 ICD study populations.³ Separate models were estimated for the class I and class IIa groups. The 2 statistical models included a series of predictive covariates that were considered likely indicators for CRT-D or that were considered likely to be associated with either mortality or risk for rehospitalization caused by HF. All covariates were selected a priori on the basis of their clinical relevance, and all selected covariates were retained in the final models.⁴

The multivariate logistic regression model's capacity to discriminate between patients with and without CRT-D was measured using the C-statistic.⁵ A C-statistic of 0.5 indicates that the model provides no predictive discrimination, while a value of 1.0 indicates perfect discrimination between patients with CRT-D and those with ICDs only. The proportion of the total variation in the probability of CRT-D accounted for by the model was assessed using Nagelkerke's R^2 statistic. Values of Nagelkerke's R^2 statistic range from 0 for models that provide no predictive information to 1 for models that predict perfectly.⁶ The Wald chi-square test statistic was used to measure the relative contribution of each individual covariate included in the model toward the overall performance of the model.

Every patient with CRT-D was matched to a patient in the group with standard ICDs (ICD only) with the closest propensity score (probability of receiving CRT-D). Some patients with ICD only were matched more than once to patients in the CRT-D patient group. All covariates included in the propensity score model were assessed for their distributional balance between the CRT-D and matched ICD-only groups. Differences in the distribution of propensity score covariate values between patients in the CRT-D and ICD-only groups were assessed for statistical significance using bivariate logistic regression analysis to calculate the Wald chi-square test statistic for the association between group status and covariate values.

Cox proportional-hazards regression analysis was used to estimate differences in mortality risk up to 4 years after implantation surgery, between patients with CRT-D and those with ICDs only. Survival functions for the CRT-D patient group and for the matched cohort of patients from the ICD-only group were estimated with stratification on the matched pairs, to account for the matched nature of the study data.^{7,8}

Competing risks analysis was used to estimate differences in the risk for rehospitalization caused by HF up to 4 years after implantation surgery. Because some patients may die

without previous HF hospitalization, analysis of HF hospitalization events after implantation requires adjustments for differences in the occurrence of death as a competing event.^{9–11} Competing risks analysis using the semiparametric proportional-hazards model was used to compare CRT-D and ICD-only patients with regard to their risk for HF hospitalization.¹²

The sensitivity of the results to a potentially missing confounder was assessed by repeating the complete analysis using a revised propensity score model that excluded a highly significant covariate in the original model.¹³ We also assessed the sensitivity of the results to the inclusion of additional adjustments for patient differences in the propensity score–balanced groups. Some studies using propensity scores include the individual covariates used to derive the propensity scores as additional adjustment covariates in the comparison of patient outcomes.^{14,15} The original comparison of survival in the matched population using Cox proportional-hazards regression analysis was repeated, including each of the covariates originally used to estimate the probability of receiving CRT-D as additional covariates. The competing risks analysis was also repeated, including a subset of covariates expected to contribute the most to the statistical performance of the model.

Results

The ICD registry included 6,496 patients with CRT-D and 2,079 patients with ICDs only who met class I recommendations for CRT. The multivariate logistic regression model used to calculate the probability of CRT-D for these patients achieved adequate statistical performance, obtaining a C-statistic of 0.76 and a Nagelkerke's R^2 value of 0.25. Table 1 lists each of the 35 covariates included in the propensity score model, along with the Wald chi-square test statistic values and associated p values for each covariate. The Wald chi-square test statistic values demonstrate that the covariates NYHA class, implantation personnel type, facility type, history of ventricular arrhythmias, use of diuretics, and use of angiotensin receptor blockers were leading individual contributors to the predictive performance of the model. Lists of the specific value distributions for each covariate are available from the authors in a Supplementary Table.

The distributions of covariate values between patients in the CRT-D and matched ICD-only groups were balanced for most of the covariates included in the propensity score model. Statistically significant differences ($p < 0.01$) occurred for 10 of the 35 covariates included in the propensity score model. Only 2 of these covariates were significant predictors of CRT-D: chronic kidney disease and the use of angiotensin receptor blocker. Patients with 8 matches to patients in the CRT-D group accounted for 54% of the patients in the ICD-only group. The absolute difference in propensity scores between matched pairs was < 0.005 for 99.8% of the matched population.

Table 2 presents hazard ratios (HRs) for the difference in the risk for death with CRT-D compared with that for patients in the ICD-only group, for patients who met class I recommendations. The relative hazard of death was significantly lower for patients with CRT-D (HR 0.83). These results were not sensitive to the potential effects of a missing covariate in the propensity score model. Nearly equivalent results were obtained by repeating the complete analysis, with adjustments for history of ventricular arrhythmia

(Wald chi-square 27.9, $p < 0.0001$) excluded from the propensity score model (HR 0.82). Repeating the analysis with supplemental adjustments for the effects of all covariates included in the propensity score model yielded results similar to the original comparison (HR 0.87). Figure 1 illustrates the cumulative incidence of death over the 4 years of available follow-up after implantation for patients with CRT-D or ICDs only in the class I study population.

Table 2 also presents HRs for the difference in the risk for HF-related hospitalization with CRT-D compared with that for patients in the ICD-only group, for patients who met class I recommendations. In the competing risks analysis, patients with CRT-D were demonstrated to have significantly lower risks for rehospitalization for HF occurring any time during the available period of follow-up (HR 0.88), after accounting for differences in survival between groups. These results were not sensitive to a potential missing confounder, as similar results were obtained by repeating the analysis with adjustments for history of ventricular arrhythmia excluded from the propensity score model (HR 0.82). The analysis was repeated using supplemental adjustments for 10 key covariates included in the propensity score model (NYHA class, QRS duration, the LVEF, systolic blood pressure, diastolic blood pressure, heart rate, HF duration, history of ventricular arrhythmia, angiotensin receptor blocker use, and receipt of diuretics). Results from the sensitivity analysis were nearly equivalent to the original results. Patients with CRT-D had significantly lower risks for HF hospitalization occurring any time during the available period of follow-up (HR 0.88). Figure 1 illustrates the cumulative incidence of HF hospitalization for patients with CRT-D or ICDs only in the class I study population, adjusted for differences in survival.

There were 5,984 patients with CRT-D and 2,583 patients with ICDs only who met class IIa recommendations for CRT. The propensity score model used to estimate the probability of CRT-D in the class IIa patient group included 36 covariates. The model achieved adequate statistical performance, obtaining a C-statistic of 0.74 and a Nagelkerke's R^2 value of 0.23. In the class IIa patient group model, NYHA class, left bundle branch block morphology, and QRS interval group were the top 3 contributors to model performance. Table 1 lists the Wald chi-square test statistic values and associated p values for each covariate included in the propensity score model. Statistically significant differences ($p < 0.01$) in the balance of covariate values between groups occurred for only 2 of the 36 covariates. Patients matched from 1 to 6 times in the ICD-only group represented 55% of the total group. The absolute difference in propensity scores between matched pairs was < 0.005 for 99.9% of the matched population.

Table 3 presents HRs for the difference in the risk for death with CRT-D compared with that for patients in the ICD-only group, for patients who met class IIa recommendations. The relative hazard of death was lower for patients with CRT-D (HR 0.90) compared with ICDs only, although the amount of the reduction in risk was smaller than in the class I sub-population. Nearly equivalent results were obtained by repeating the complete analysis, with adjustments for history of ventricular arrhythmia (Wald chi-square 18.4, $p < 0.0001$) excluded from the propensity score model. Repeating the analysis with supplemental adjustments for all covariates included in the propensity score model also demonstrated that there was a significant reduction in mortality risk (HR 0.93). Figure 2 illustrates the

cumulative incidence of death over the 4 years of available follow-up for patients with CRT-D or ICDs only in the class IIa study population.

For patients in the Class IIa subpopulation, there was no significant difference in the risk for rehospitalization for HF occurring any time during the available period of follow-up between patients with CRT-D and the matched group with ICD only (HR 1.03, $p = 0.2600$). Repeating the analysis, first with adjustments for history of ventricular arrhythmia excluded from the propensity score model and second by controlling for 10 key predictive covariates included in the propensity score model (NYHA class, left bundle branch block, QRS duration, the LVEF, systolic blood pressure, diastolic blood pressure, HF duration, history of ventricular arrhythmia, angiotensin receptor blocker use, and receipt of diuretics) yielded results nearly equivalent to the original results (HR 0.97 and HR 1.02, respectively). Figure 2 illustrates the cumulative incidence of HF hospitalization for surviving patients with CRT-D or ICDs only who met class IIa recommendations for CRT.

Discussion

This analysis of the Medicare patient population demonstrates that the greatest benefit with CRT-D was observed in patients with guideline-based class I recommendations for CRT-D. In these patients, CRT-D was associated with a 17% reduction in risk for death and a 12% reduction in risk for HF hospitalization compared with a standard ICD. In patients with class IIa recommendations, there was also a significant reduction in risk for death during follow-up (10%), but the risk for HF hospitalization was not significantly different for patients receiving CRT-D versus standard ICDs.

These findings are particularly relevant to how the community of cardiovascular disease professionals interpret the comparative effectiveness of treatments. Clinical trials are the gold standard for demonstrating therapeutic efficacy. However, real-world differences in treatment protocols and patient selection yield substantial differences between the practice setting and clinical trial setting. Although not perfect, a thorough propensity score analysis provides a reliable assessment of the comparative effectiveness of therapy alternatives on patient outcomes observed in clinical practice. The effect sizes for CRT-D versus standard ICDs in the present study, particularly with respect to overall survival, although significant, were smaller than those reported in clinical trials.^{16,17} In addition, these results demonstrate that effect sizes for patients with guideline-based class I indications for CRT-D are greater than those for class IIa implantation indications. With respect to the outcome of improved survival with CRT-D, this may be expected to include a reduction in pump-failure deaths and deaths related to ventricular tachycardia or ventricular fibrillation on the basis of the antiarrhythmic effect of CRT-induced improvements in cardiac function.¹⁸ However, the study design did not permit differentiation between arrhythmic and pump-failure deaths.

The conclusions generated from the present analysis are supported by the high-quality method used in the analysis, and several points are noteworthy in this regard. First, the propensity matching was based on 35 covariates. With respect to these covariates, it is remarkable that a significant proportion of patients with NYHA class II status underwent CRT-D implantation in this registry, although the guidelines at that time recommended that

implantation in patients with NYHA class III and IV status. Second, the comparison groups were very well matched, with most covariates showing no significant differences (on the basis of a p value of 0.01) between the groups, which is remarkable for such a large cohort. In addition, the absolute difference in propensity scores between matched pairs was <0.005 for 99.8% of the matched population. Third, results are based on >4 years of follow-up for all patients. Fourth, the outcomes assessed included not only death but also HF hospitalizations. Fifth, to analyze appropriately the hazard for HF hospitalization as a competing risk relative to death, the robust and computationally intensive competing risks analysis method was used to determine individual hazards appropriately. Sixth, a sensitivity analysis was applied to ensure that key covariates did not have an undue influence on the results. On the basis of these methodologic features, the present analysis provides highly relevant results to clinical cardiologists regarding the improvement in outcomes they might expect their patients to experience in clinical practice as a result of CRT-D, as well as how these outcomes differ on the basis of the strength of the guideline-based recommendation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. (A) Plot of the cumulative incidence of death over the 4 years of available follow-up for surviving patients with CRT-D or ICDs only who met class I recommendations for CRT. (B) Plot of the cumulative incidence of HF hospitalization in this patient population, accounting for the competing risk for death.

Figure 2.

(A) Plot of the cumulative incidence of death over the 4 years of available follow-up for surviving patients with CRT-D or ICDs only who met class IIa recommendations for CRT.
(B) Plot of the cumulative incidence of HF hospitalization in this patient population, accounting for the competing risk for death.

Table 1
Statistical significance of propensity score covariates and matched group differences

	Class I			Class IIa		
	Wald Chi-Square Test Statistic	Wald Chi-Square p-Value	Significance of Matched Group Difference	Wald Chi-Square Test Statistic	Wald Chi-Square p-Value	Significance of Matched Group Difference
Left Bundle Branch Block	n.a.	n.a.	n.a.	40.78	<0.0001	0.5344
NYHA Class	1116.16	<0.0001	0.1860	949.02	<0.0001	0.5576
QRS Interval group	10.81	0.1471	0.1516	40.43	<0.0001	0.0052
Left Ventricular Ejection Fraction	6.28	0.0122	0.6079	12.31	0.0005	0.9646
Systolic Blood Pressure	3.06	0.0803	0.1324	1.22	0.2694	0.5937
Diastolic Blood Pressure	0.63	0.4288	0.4317	0.08	0.7815	0.0271
Heart Rate	0.02	0.9011	0.2385	2.10	0.1478	0.0989
Duration of Heart Failure in months	5.71	0.0168	0.2360	7.28	0.0070	0.6038
Ischemic Cardiomyopathy	5.84	0.0157	0.0438	0.37	0.5413	0.4575
High Risk Inherited Condition	4.14	0.0420	0.0386	4.70	0.0302	0.0302
Gender	0.08	0.7743	0.0045	0.16	0.6901	0.5241
Age Group	4.54	0.6035	0.0090	1.37	0.9674	0.3334
Chronic Kidney Disease	8.87	0.0029	<0.0001	8.00	0.0047	0.4625
Prior Coronary Artery Bypass Graft	0.00	0.9499	0.4260	1.46	0.2265	0.2681
Ventricular Arrhythmias	27.90	<0.0001	0.8544	18.40	<0.0001	0.0428
Diabetes	0.06	0.8121	0.0227	0.19	0.6639	0.4149
Myocardial Infarction	4.32	0.0376	0.1989	0.20	0.6525	0.3049
Sudden Cardiac Arrest	0.60	0.4399	0.4866	2.14	0.1431	0.1158
Angina Pectoris	1.69	0.1932	0.1540	0.08	0.7770	0.8437
Atrial Fibrillation	0.13	0.7145	0.2027	0.39	0.5333	0.5797
Coronary Artery Disease	0.85	0.3574	0.1858	4.84	0.0278	0.9231
Hypertension	0.85	0.3555	0.3699	0.58	0.4467	0.8802
Angioplasty	0.34	0.5595	<0.0001	0.80	0.3711	0.6255
Pacemaker	3.03	0.0818	0.3570	10.25	0.0014	0.1351
Cancer	0.58	0.4453	0.0056	1.11	0.2922	0.6080
Cigarette Smoker	3.69	0.1577	<0.0001	6.19	0.0453	0.7149

	Class I			Class IIa		
	Wald Chi-Square Test Statistic	Wald Chi-Square p-Value	Significance of Matched Group Difference	Wald Chi-Square Test Statistic	Wald Chi-Square p-Value	Significance of Matched Group Difference
Beta Blocker	3.16	0.0755	0.0078	0.89	0.3446	0.0015
ACE Inhibitor	2.77	0.0962	0.0008	0.96	0.3284	0.5523
Angiotensin Receptor Blocker	13.30	0.0003	<0.0001	3.62	0.0569	0.0167
Digoxin	0.71	0.3991	0.8732	7.18	0.0074	0.1158
Diuretic	20.54	<0.0001	0.2793	13.10	0.0003	0.7388
Amiodarone	4.47	0.0345	0.0022	7.09	0.0077	0.4441
Sotalol	0.04	0.8439	0.9078	1.00	0.3173	0.7136
Coumadin	1.04	0.3067	0.0899	1.04	0.3090	0.0884
Type of Implant Personnel	28.89	<0.0001	0.1368	35.16	<0.0001	0.3105
Type of Facility	25.83	<0.0001	0.3004	40.49	<0.0001	0.0869

Table 2

Risk of all cause death or heart failure hospitalization in the CRT-D registry group compared to the propensity score matched ICD only group for class I patients

	Hazard Ratio	95% C.I.	p-Value
All cause death over 4 years of follow-up			
CRT-D compared to matched ICD group	0.83	(0.77–0.88)	<0.0001
CRT-D compared to matched ICD group, estimated using original propensity score model with excluded covariate	0.82	(0.77–0.88)	<0.0001
CRT-D compared to matched ICD group, estimated with concurrent adjustments for covariates used in propensity score model	0.87	(0.81–0.94)	0.0002
Hospitalization for heart failure over 4 years of follow-up			
CRT-D compared to matched ICD group	0.88	(0.83–0.94)	<0.0001
CRT-D compared to matched ICD group, estimated using original propensity score model with excluded covariate	0.82	(0.77–0.87)	<0.0001
CRT-D compared to matched ICD group, estimated with concurrent adjustments for covariates used in propensity score model	0.88	(0.83–0.93)	<0.0001

Table 3

Risk of all cause death or heart failure hospitalization in the CRT-D registry group compared to the propensity score matched ICD only group for class IIa patients

	Hazard Ratio	95% C.I.	p-Value
All cause death over 4 years of follow-up			
CRT-D compared to matched ICD group	0.90	(0.85–0.96)	0.0015
CRT-D compared to matched ICD group, estimated using original propensity score model with excluded covariate	0.91	(0.86–0.97)	0.0050
CRT-D compared to matched ICD group, estimated with concurrent adjustments for covariates used in propensity score model	0.93	(0.86–0.99)	0.0452
Hospitalization for heart failure over 4 years of follow-up			
CRT-D compared to matched ICD group	1.03	(0.97–1.10)	0.2600
CRT-D compared to matched ICD group, estimated using original propensity score model with excluded covariate	0.97	(0.91–1.03)	0.3200
CRT-D compared to matched ICD group, estimated with concurrent adjustments for covariates used in propensity score model	1.02	(0.96–1.09)	0.4700