Comparative Effectiveness of Cardiac Resynchronization Therapy Defibrillators Versus Standard Implantable Defibrillators in Medicare Patients

Robbert Zusterzeel, MD[a], Daniel A. Caños, MPH, PhD[a], William E. Sanders, MD, MBA[a], Henry Silverman, BS[b], Thomas E. MaCurdy, PhD[b], Christopher M. Worrall, BS[c], Jeffrey Kelman, MD, MMSc[c], Danica Marinac-Dabic, MD, PhD[a], and David G. Strauss, MD, PhD[a,*]

Previous analyses have shown that there is lower mortality with cardiac resynchronization therapy defibrillators (CRT-D) in patients with left bundle branch block (LBBB) but demonstrated mixed results in patients without LBBB. We evaluated the comparative effectiveness of CRT-D versus standard implantable defibrillators (ICDs) separately in patients with LBBB and right bundle branch block (RBBB) using Medicare claims data. Medicare records from CRT-D and ICD recipients from 2002 to 2009 that were followed up for up to 48 months were analyzed. We used propensity scores to match patients with ICD to those with CRT-D. In LBBB, 1:1 matching with replacement resulted in 54,218 patients with CRT-D and 20,763 with ICD, and in RBBB, 1:1 matching resulted in 7,298 patients with CRT-D and 7,298 with ICD. In LBBB, CRT-D had a 12% lower risk of heart failure hospitalization or death (hazard ratio [HR] 0.88, 95% confidence interval 0.86 to 0.90) and 5% lower death risk (HR 0.95, 0.92 to 0.97) compared with ICD. In RBBB, CRT-D had a 15% higher risk of heart failure hospitalization or death (HR 1.15, 1.10 to 1.20) and 13% higher death risk (HR 1.13, 1.07 to 1.18). Sensitivity analysis revealed that accounting for covariates not captured in the Medicare database may lead to increased benefit with CRT-D in LBBB and no difference in RBBB. In conclusion, in a large Medicare population, CRT-D was associated with lower mortality in LBBB but higher mortality in RBBB. The absence of certain covariates, in particular those that determine treatment selection, may affect the results of comparative effectiveness studies using claims data. Published by Elsevier Inc. (Am J Cardiol 2015;116:79−84)

Cardiac resynchronization therapy (CRT), either alone or in combination with an implantable cardioverter defibrillator (ICD, CRT-D), is an increasingly used therapy for heart failure and has been shown to reduce heart failure symptoms, heart failure hospitalizations, and mortality while improving quality of life.[1−3] Current professional society guidelines for CRT give a class I indication to patients with left bundle branch block (LBBB) and a QRS duration $\geq$150 ms, whereas patients without LBBB receive either a class IIa or class IIb recommendation.[4] Recent analyses from pre-market clinical trials and post-market registry data demonstrated that there, indeed, is a significantly lower mortality with CRT-D in patients with LBBB but that there is no reduced mortality in patients with solely right bundle branch block (RBBB).[5−7] Although registry data are very useful for answering questions that cannot be answered with pre-market data alone, in some situations, registry data may not be available. In these cases, claims data may then be useful to assess long-term outcomes in large real-world populations. We evaluated the comparative effectiveness of CRT-D versus ICD separately in patients with LBBB and RBBB using Medicare claims data.

Methods

This study was approved by the US Food and Drug Administration (USFDA) Research in Human Subjects Committee and the Centers for Medicare and Medicaid Services (CMS). It included all Medicare patients who received a primary prevention CRT-D (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] procedure code "00.51") or ICD device (*ICD-9-CM* procedure code "37.94") from July 1, 2002, to September 30, 2009, who were also continuously enrolled in Medicare Part A (inpatient hospital coverage) and B (outpatient medical coverage) $\geq$12 months before implantation. The following patients were excluded from further analysis: patients with an *ICD-9* code for ventricular fibrillation, ventricular flutter, cardiac arrest, or sudden cardiac arrest as part of secondary prevention and patients with end-stage renal disease or hypertrophic cardiomyopathy (Supplementary Methods).

[a]Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, Maryland; [b]Acumen, LLC, SafeRx, Burlingame, California; and [c]Centers for Medicare and Medicaid Services, Baltimore, Maryland. Manuscript received March 2, 2015; revised manuscript received and accepted March 26, 2015.

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*Corresponding author: Tel: (301) 796-6323; fax: (301) 796-9927.
E-mail address: david.strauss@fda.hhs.gov (D.G. Strauss).

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Table 1
Baseline characteristics of left bundle branch block and right bundle branch block patients after propensity score matching

	Matched Left Bundle Branch Block					Matched Right Bundle Branch Block				
	CRT-D		ICD		SMD	CRT-D		ICD		SMD
	N	%	N	%		N	%	N	%	
Variable	**54,218**		**20,763**			**7,298**		**7,298**		
Male	36,357	67%	13,877	67%	0.01	6,218	85%	6,217	85%	0.00
Age (years)										
0-64	5,625	10%	2,181	11%	0.00	758	10%	771	11%	0.01
65-69	8,625	16%	3,348	16%	0.01	1,123	15%	1,129	16%	0.00
70-74	12,319	23%	4,733	23%	0.00	1,634	22%	1,628	22%	0.00
75-79	13,915	26%	5,259	25%	0.01	1,901	26%	1,872	26%	0.01
80-84	10,065	19%	3,846	19%	0.00	1,401	19%	1,436	20%	0.01
85+	3,669	7%	1,393	7%	0.00	481	7%	462	6%	0.01
Black	4,418	8%	1,755	9%	0.01	591	8%	594	8%	0.00
Other	1,616	3%	620	3%	0.00	250	3%	246	3%	0.00
White	48,184	89%	18,386	89%	0.01	6,457	89%	6,458	89%	0.00
Charlson Score 0	639	1%	212	1%	0.02	70	1%	63	1%	0.00
Charlson Score 1	5,931	11%	2,306	11%	0.01	537	7%	517	7%	0.01
Charlson Score 2	9,649	18%	3,756	18%	0.01	1,044	14%	1,025	14%	0.01
Charlson Score 3	10,625	20%	4,027	19%	0.01	1,397	19%	1,410	19%	0.00
Charlson Score 4+	27,374	51%	10,461	50%	0.00	4,250	58%	4,283	59%	0.01
Diabetes Mellitus	25,482	47%	9,745	47%	0.00	3,776	52%	3,791	52%	0.00
Mitral or Aortic Valve Disorder	31,642	58%	12,047	58%	0.01	4,217	58%	4,181	57%	0.01
Hypertension	47,407	87%	18,144	87%	0.00	6,540	90%	6,523	89%	0.01
Myocardial Infarction	21,299	39%	8,171	39%	0.00	3,871	53%	3,875	53%	0.00
Coronary Heart Disease	32,445	60%	12,449	60%	0.00	4,979	68%	4,962	68%	0.00
Tricuspid or Pulmonary Valve Disorder	8,734	16%	3,408	16%	0.01	1,273	17%	1,273	17%	0.00
Atrial Fibrillation	24,630	45%	9,299	45%	0.01	3,691	51%	3,664	50%	0.01
Prior Heart Failure Hospitalization	15,826	29%	6,024	29%	0.00	2,013	28%	1,934	27%	0.02
Prior Stroke	2,724	5%	1,063	5%	0.00	462	6%	462	6%	0.00
Peripheral Vascular disease	11,965	22%	4,652	22%	0.01	2,000	27%	2,000	27%	0.00
Ventricular Tachycardia	19,236	36%	7,348	35%	0.00	3,310	45%	3,283	45%	0.01
Percutaneous Coronary Intervention	1,888	4%	686	3%	0.01	416	6%	411	6%	0.00
Coronary Bypass	5,047	9%	1,921	9%	0.00	971	13%	975	13%	0.00

The presence of preexisting co-morbidities and other covariates (Table 1) was assessed through *ICD-9* codes in a 12-month look-back window, whereas demographics were determined using the Medicare enrollment database. To account for other competing factors for death, we also included the Charlson co-morbidity score. The Charlson score is a score to predict 10-year mortality based on whether a patient has certain health conditions[8]; further explanation can be found in the Supplementary Methods.

To further specify the cohort to only include incident patients with CRT-D and ICD with LBBB or RBBB and a primary prevention implant, we used *ICD-9* procedure codes and current procedural terminology codes used for maintenance and follow-up of patients with CRT-D and ICD devices (patients without an *ICD-9* code for LBBB or RBBB were excluded). Patients were excluded if they either had a maintenance code or a cohort-defining event (CRT-D or ICD implantation code) in the 12 months before implantation, indicating a previous device implant. All codes used for cohort determination and the assessment of preexisting comorbidities can be found in the Supplementary Appendix.

The defined end points for this study were (1) heart failure hospitalization or death and (2) all-cause mortality. All-cause mortality was determined using the Medicare Master Beneficiary Summary File from CMS, which documents the date of death for all enrolled patients assessed from the Social Security Administration. Heart failure hospitalization was defined as having an *ICD-9* code for heart failure as the primary diagnosis on an inpatient claim. Patients were censored if they did not reach the end point after a maximum of 48 months of follow-up or if they were no longer continuously enrolled in Medicare Part B.

Propensity score matching was performed separately in patients with LBBB and RBBB to reduce potential treatment selection bias and differences in baseline characteristics between patients with CRT-D and ICD. A multivariable logistic regression model including all variables listed in Table 1 was used to calculate the propensity score. Patients with LBBB ICD were 1:1 matched (with replacement) to those with LBBB CRT-D, and patients with RBBB ICD were 1:1 matched to those with RBBB CRT-D using a 0.1 caliper width. Standardized mean differences (SMD) were calculated to ensure that there were no significant differences between patients with CRT-D and ICD. Treatment groups were considered balanced when the standardized mean difference was <0.10 as this has been taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups.[9] Kaplan-Meier curves and multivariable Cox proportional hazards models were generated to compare

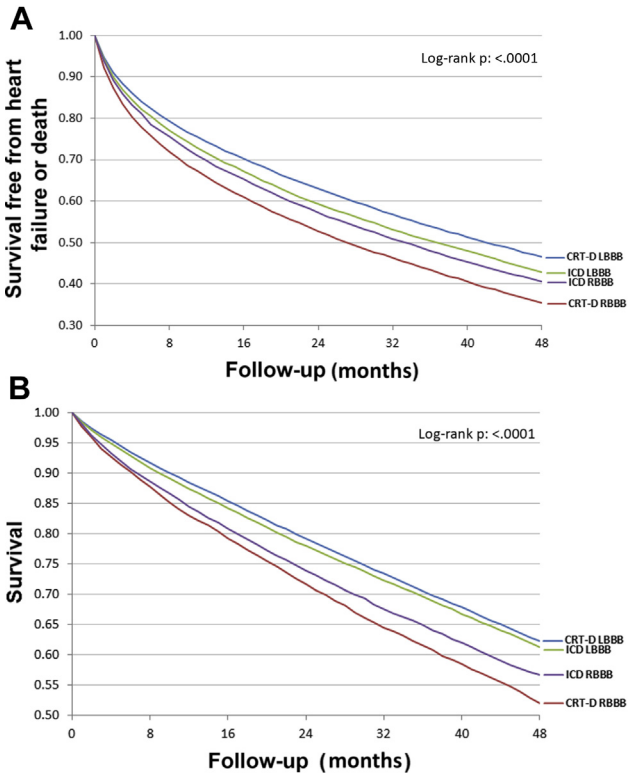

Figure 1. *(A)* Kaplan-Meier graphs of freedom from heart failure hospitalization or death in propensity score−matched patients with LBBB and RBBB. *(B)* Kaplan-Meier graphs of survival in propensity score−matched patients with LBBB and RBBB.

the effect of CRT-D to ICD in patients with both LBBB and RBBB. We also performed sensitivity analyses for both end points to investigate the potential influence of unmeasured variables because, contrary to registry databases, important cardiac confounders, such as New York Heart Association (NYHA) heart failure class, ejection fraction, and QRS duration, are not available in Medicare claims data (Supplementary Appendix). Statistical analyses were performed using SAS Statistical Software (version 9.3; SAS Institute, Cary, North Carolina) and STATA (version 11; StataCorp, College Station, Texas). All reported 95% confidence intervals (CIs) and p values are 2 sided.

Results

After propensity score matching, the cohort consisted of 54,218 patients with CRT-D and 20,763 with ICD in LBBB and 7,298 patients with CRT-D and 7,298 with ICD in RBBB. There were no significant differences between CRT-D and ICD treatment groups in LBBB or RBBB, indicating that they were properly balanced (Table 1). However, there were some differences between the matched LBBB and RBBB populations. Patients with RBBB more often were men, had diabetes, previous myocardial infarction, coronary heart disease, atrial fibrillation, peripheral vascular disease, ventricular tachycardia, a higher Charlson score, a higher percutaneous coronary intervention, and coronary bypass procedure rate compared with those with LBBB. Follow-up data were available for a median of 32 months in LBBB and 24 months in RBBB.

The rate of heart failure hospitalization or death was lower in patients with LBBB compared with those with RBBB (51.2% vs 58.6%). In LBBB, unadjusted heart failure hospitalization or death was lower for CRT-D than ICD (50.1% vs 54.0%), whereas this relation was reversed in patients with RBBB (60.8% vs 56.4%) (Figure 1).

Multivariable-adjusted Cox proportional hazards models were determined separately in patients with LBBB and RBBB. In LBBB, patients with CRT-D had a 12% lower risk for heart failure hospitalization or death (hazard ratio [HR] 0.88, 95% CI 0.86 to 0.90) compared with ICD, whereas in RBBB, patients with CRT-D had a 15% higher risk (HR = 1.15, 1.10 to 1.20) than those with ICD (Table 2).

Similar results as for the combined end point of heart failure hospitalization or death were observed for the end point of all-cause mortality. After a maximum follow-up of 48 months, 32,317 patients (36.1% of the combined LBBB and RBBB matched populations) had died and all-cause mortality was lower in patients with LBBB compared with those with RBBB (34.9% vs 42.3%). In LBBB, the unadjusted mortality rate was lower in patients with CRT-D than those with ICD (40.3% vs 44.2%), whereas in RBBB this was reversed demonstrating a higher mortality rate in patients with CRT-D than those with ICD (35.8% vs 34.5%) (Figure 1).

Multivariable-adjusted models showed that in LBBB, patients with CRT-D had a 5% lower risk of death than those with ICD (HR = 0.95, 0.92 to 0.97), whereas in RBBB, patients with CRT-D had a 13% higher death risk (HR = 1.13, 1.07 to 1.18) compared with those with ICD (Table 2).

Sensitivity analyses introducing an unobserved covariate into the already matched LBBB and RBBB populations were conducted to evaluate the potential influence of covariates not captured in the Medicare claims database. As an example, using previously published analyses,[10,11] we determined hypothetical numbers to be imputed into our sensitivity analyses. When accounting for NYHA class in CRT-D versus ICD, we observed that there may be an even lower mortality risk with CRT-D in LBBB and no difference between CRT-D and ICD in RBBB (Supplementary Appendix).

Discussion

The findings of this study suggest that in propensity score−matched Medicare cohorts, CRT-D (compared with ICD) is associated with a 12% lower risk of heart failure hospitalization or death and 5% lower mortality in patients with LBBB, whereas in those with RBBB, there is a 15% higher risk of heart failure hospitalization or death and 13% higher mortality. These results are different from large registry studies, in which it was shown that the mortality risk difference with CRT-D compared with ICD in LBBB was much lower than observed in the current analysis and that there was no mortality difference between CRT-D and ICD in RBBB. The sensitivity analysis in this study, indeed, suggests that accounting for unmeasured covariates in claims data may lead to an even lower mortality HR in LBBB and no mortality risk difference between CRT-D and ICD in RBBB.

Table 2
Multivariable models for endpoints in left- and right bundle branch block

Covariates	Heart Failure Hospitalization or Death						All-Cause Mortality					
	Left Bundle Branch Block			Right Bundle Branch Block			Left Bundle Branch Block			Right Bundle Branch Block		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
CRT-D	0.88	0.86-0.90	<0.001	1.15	1.10-1.20	<0.001	0.95	0.92-0.97	<0.001	1.13	1.07-1.18	<0.001
ICD	Ref			Ref			Ref			Ref		
Male	1.11	1.08-1.13	<0.001	0.91	0.86-0.97	0.002	1.27	1.24-1.31	<0.001	1.02	0.95-1.09	0.59
Age (years)												
0-64	1.21	1.16-1.26	<0.001	1.11	1.02-1.22	0.017	1.07	1.01-1.13	0.020	0.99	0.88-1.10	0.81
65-69	Ref			Ref			Ref			Ref		
70-74	1.04	1.01-1.08	0.019	0.995	0.92-1.07	0.89	1.11	1.06-1.16	<0.001	1.06	0.97-1.16	0.22
75-79	1.17	1.13-1.21	<0.001	1.12	1.04-1.20	0.002	1.35	1.30-1.41	<0.001	1.28	1.18-1.40	<0.001
80-84	1.35	1.30-1.40	<0.001	1.32	1.23-1.43	<0.001	1.65	1.58-1.72	<0.001	1.54	1.41-1.68	<0.001
85+	1.64	1.57-1.71	<0.001	1.54	1.40-1.70	<0.001	2.18	2.07-2.30	<0.001	2.01	1.80-2.24	<0.001
Black	1.34	1.29-1.39	<0.001	1.35	1.25-1.45	<0.001	1.12	1.07-1.17	<0.001	1.05	0.95-1.15	0.34
Other	1.18	1.12-1.25	<0.001	1.01	0.90-1.14	0.87	1.05	0.98-1.13	0.17	0.92	0.80-1.06	0.26
White	Ref			Ref			Ref			Ref		
Charlson Score 0	0.79	0.68-0.91	<0.001	0.69	0.47-0.999	0.050	0.70	0.57-0.85	<0.001	0.76	0.48-1.20	0.24
Charlson Score 1	Ref			Ref			Ref			Ref		
Charlson Score 2	1.21	1.15-1.27	<0.001	1.39	1.23-1.57	<0.001	1.27	1.19-1.35	<0.001	1.39	1.20-1.62	<0.001
Charlson Score 3	1.33	1.27-1.40	<0.001	1.61	1.43-1.81	<0.001	1.46	1.37-1.54	<0.001	1.71	1.48-1.98	<0.001
Charlson Score 4+	1.77	1.69-1.85	<0.001	2.20	1.96-2.47	<0.001	2.06	1.94-2.18	<0.001	2.56	2.22-2.95	<0.001
Diabetes Mellitus	1.14	1.11-1.16	<0.001	1.09	1.04-1.14	<0.001	1.10	1.07-1.13	<0.001	1.02	0.97-1.08	0.50
Mitral or Aortic Valve Disorder	1.07	1.05-1.10	<0.001	1.11	1.06-1.17	<0.001	1.10	1.07-1.13	<0.001	1.12	1.06-1.19	<0.001
Hypertension	0.97	0.94-1.01	0.13	0.96	0.89-1.04	0.31	0.86	0.83-0.89	<0.001	0.91	0.83-0.999	0.029
Myocardial Infarction	1.06	1.04-1.08	<0.001	0.96	0.92-1.01	0.12	1.01	0.99-1.04	0.42	0.94	0.89-0.990	0.017
Coronary Heart Disease	1.17	1.14-1.19	<0.001	1.10	1.05-1.16	<0.001	1.18	1.15-1.21	<0.001	1.07	1.01-1.13	0.017
Tricuspid or Pulmonary Valve Disorder	1.05	1.02-1.08	<0.001	1.02	0.97-1.08	0.41	1.06	1.03-1.10	0.001	1.00	0.94-1.07	0.94
Atrial Fibrillation	1.29	1.27-1.32	<0.001	1.24	1.18-1.29	<0.001	1.29	1.26-1.32	<0.001	1.24	1.18-1.31	<0.001
Prior Heart Failure Hospitalization	1.69	1.65-1.72	<0.001	1.87	1.78-1.96	<0.001	1.53	1.49-1.57	<0.001	1.65	1.57-1.75	<0.001
Stroke	1.06	1.02-1.11	0.007	1.03	0.94-1.11	0.56	1.10	1.04-1.15	<0.001	1.03	0.94-1.13	0.55
Peripheral Vascular disease	1.16	1.13-1.19	<0.001	1.12	1.07-1.18	<0.001	1.19	1.16-1.22	<0.001	1.18	1.12-1.24	<0.001
Ventricular Tachycardia	1.21	1.18-1.23	<0.001	1.09	1.04-1.14	<0.001	1.22	1.19-1.25	<0.001	1.12	1.06-1.18	<0.001
Percutaneous Coronary Intervention	0.65	0.62-0.69	<0.001	0.68	0.62-0.75	<0.001	0.57	0.53-0.62	<0.001	0.58	0.51-0.65	<0.001
Coronary Bypass	0.93	0.89-0.96	<0.001	0.96	0.90-1.02	0.15	0.84	0.80-0.87	<0.001	0.85	0.79-0.92	<0.001

Previously published analyses of CRT effect in non-LBBB and RBBB have shown mixed results. That CRT can be harmful in general was demonstrated in the EchoCRT trial, which enrolled patients with systolic heart failure (ejection fraction $\leq$35%) and a QRS duration <130 ms. In that population, CRT did not reduce the rate of death or hospitalization for heart failure and actually increased mortality (HR = 1.81, 1.11 to 2.93).[12] For CRT in patients without LBBB, a recent meta-analysis,[13] substudies of clinical trials,[14–16] and single-center studies[10,17,18] have either shown a slightly lower mortality, no mortality difference, or higher mortality.

In the present analysis, patients with RBBB were generally sicker than those with LBBB and they more often had comorbidities associated with a worse response to CRT. These factors primarily include ischemic cardiomyopathy and atrial fibrillation.[19] A previous study demonstrated that in patients eligible for ICD implantation, ischemic cardiomyopathy was associated with a higher scar burden and that patients with RBBB had significantly larger scar size than those with LBBB.[20] The large myocardial scar may be 1 explanation of why patients with RBBB do worse than those with LBBB CRT-D. Also, patients with RBBB were more often men, and they have been shown to have a worse response to CRT than women.[21–24] That patients with RBBB might be sicker is also supported in the present study by a higher mortality in patients with RBBB ICD than those with LBBB ICD (40.3% vs 35.8%). However, after multivariable adjustment for all these factors in the matched populations, even after sensitivity analysis, CRT-D was still performing worse in RBBB than in LBBB, suggesting that CRT is not beneficial in patients with RBBB.

This study has several limitations including the possibility of misdiagnosis of baseline characteristics and end points because of the use of *ICD-9* codes and Medicare billing data. However, previous work has shown that adjudication of Medicare claims resulted in a change in <3% of claims.[25] Although the advantage of using claims data is the

ability to assess real-world performance in a large patient population, the results of the sensitivity analysis indicate that important covariates that are missing in claims, compared with registries, can affect the results of comparative effectiveness studies. This is particularly true for those that determine if a patient should receive a CRT-D or ICD device, such as NYHA heart failure class, QRS duration, and the ejection fraction. In addition, it is possible that the CRT-D and ICD implants included in this analysis were not a patients' first-device implant. This was minimized by cleaning the cohort for additional device maintenance codes. The 12-month look-back period did not allow for the assessment of the presence of other co-morbidities than those observed in the 12 months before the implantation date.

This study in Medicare patients shows that CRT-D is associated with a lower risk of heart failure hospitalization or death and death alone in patients with LBBB but a higher risk of both outcomes in those with RBBB. Accounting for covariates that are not captured in claims data may affect the results of CRT-D versus ICD comparative effectiveness studies.

Disclosures

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Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.03.037.

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