

Effects of Upgrade Versus De Novo Cardiac Resynchronization Therapy on Clinical Response and Long-Term Survival Results from a Multicenter Study

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Background—Benefits of cardiac resynchronization therapy (CRT) on morbidity and mortality in selected patients are well known. Although the number of upgrade procedures from single- or dual-chamber devices to CRT is increasing, there are only sparse data on the outcomes of upgrade procedures compared with de novo CRT. This study aimed to evaluate clinical response and survival in patients receiving de novo versus upgrade CRT defibrillator therapy.

Methods and Results—Prospectively collected outcome data were compared in patients undergoing de novo or upgrade CRT defibrillator implantation at 3 implant centers in Germany and Hungary. Clinical response was defined as an improvement by at least one New York Heart Association (NYHA) functional class. CRT implantation was performed in 552 consecutive patients of whom 375 underwent a de novo and 177 an upgrade procedure. Upgrade patients were more often implanted for secondary prevention, suffered more often from atrial fibrillation, chronic kidney disease, diabetes mellitus, and dyslipidemia, and had more often a non-LBBB (left bundle branch block) wide QRS complex, and lower left ventricular ejection fraction. Upgrade procedures were associated with a lower response rate compared to the de novo group (57% versus 69%, P univariate=0.008, P multivariate=0.021). During the follow-up of 37 ± 28 months, survival was worse after upgrade compared with de novo CRT defibrillator implantations (hazard ratio, 1.65; 95% confidence interval, 1.22–2.24; $P=0.001$) even after careful adjustment for important baseline variables (adjusted hazard ratio, 1.68; 95% confidence interval, 1.20–2.34; $P=0.002$) and after propensity-score matching (propensity-adjusted hazard ratio, 1.79; 95% confidence interval, 1.08–2.95; $P=0.023$).

Conclusions—Both clinical response and long-term survival were less favorable in patients undergoing CRT upgrade compared to de novo implantations. (*Circ Arrhythm Electrophysiol.* 2017;10:e004471. DOI: 10.1161/CIRCEP.116.004471.)

Key Words: cardiac resynchronization therapy ■ heart failure ■ hypertension ■ morbidity ■ mortality

The beneficial impact of newly implanted cardiac resynchronization therapy (CRT) on morbidity and mortality are well described in selected patients with heart failure.^{1–6} Patients with heart failure already fitted with a conventional pacemaker or implantable cardioverter defibrillator (ICD) system are often considered for a CRT upgrade after the new development of CRT criteria (ie, new left bundle branch block [LBBB]) or because of the need of frequent right ventricular pacing. The latest 2012 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society guidelines recommend a CRT upgrade at the time of device replacement with anticipated requirement for significant ventricular pacing as a class IIa indication for patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$.⁷ In the latest

European pacemaker and CRT guidelines from 2013, upgrade procedures from conventional pacemakers or ICDs to CRT are considered as a class I indication (level B) for heart failure patients with a New York Heart Association (NYHA) functional class of III to ambulatory IV, LVEF $\leq 35\%$, and a high percentage of ventricular pacing.⁸ Accordingly, the number of upgrade procedures from single- or dual-chamber devices to CRT is increasing. However, there is only weak scientific evidence about the outcomes of patients undergoing upgrade procedures compared with de novo CRT implantations.^{8,9}

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Accordingly, the aim of this study was to compare clinical response and long-term survival in a large cohort of

Received July 5, 2016; accepted December 13, 2016.

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The Data Supplement is available at <http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.116.004471/-/DC1>.

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Circ Arrhythm Electrophysiol is available at <http://circep.ahajournals.org>

DOI: 10.1161/CIRCEP.116.004471

WHAT IS KNOWN

- Patients with heart failure who already have a conventional pacemaker or implantable cardioverter defibrillator system are often considered for an upgrade to cardiac resynchronization therapy.
- However, there is only weak scientific evidence about outcomes after upgrade procedures compared with de novo cardiac resynchronization therapy implantations.

WHAT THE STUDY ADDS

- Both clinical response and long-term survival were less favorable in patients undergoing cardiac resynchronization therapy upgrade compared with de novo implantations in this large multicenter observational study.
- Findings were consistent even after careful adjustment for possible confounders using multivariate Cox regression analysis or propensity score matching.
- Our observations need to be considered when counseling individual patients on an upgrade to cardiac resynchronization therapy.

consecutive patients receiving either de novo or upgrade CRT defibrillator (CRT-D) therapy.

Methods

Patient Population

Implantation and outcome data were prospectively collected from consecutive patients undergoing CRT-D implantation at the J.W. Goethe University (Frankfurt, Germany), at the Evangelical Hospital Bielefeld (Bielefeld, Germany), and at the Medical Centre, Hungarian Defence Forces (Budapest, Hungary). CRT was considered for patients on optimized medical treatment with heart failure of NYHA functional class from II to IV, LVEF of $\leq 35\%$, and QRS width of >120 ms (de novo group).⁸ Furthermore, patients with previously implanted pacemakers or ICDs who developed the above-mentioned criteria with or without need for continuous ventricular pacing were also considered for CRT (upgrade group). The study was approved by the institutional review board of the J.W. Goethe University and complies with the ethical guidelines of the Declaration of Helsinki.

Device Implantation

CRT-ICDs from various manufacturers were used (Biotronik, Germany; ELA/Sorin, Italy; Guidant/Boston Scientific, Marlborough, MA; Medtronic, Minneapolis, MN; St. Jude Medical, St. Paul, MN) after standard indications for primary or secondary prophylaxis of sudden cardiac death. Left ventricular leads were implanted transvenously, preferably the lateral or posterolateral vein or a side-branch in close proximity to the posterolateral area, avoiding apical positions as suggested in the guidelines.⁸ In case of unsuccessful attempts of coronary sinus lead implantation, an epicardial approach was used as a separate procedure. Patients were followed-up in the outpatient clinic of participating hospitals in 6 months' intervals or when clinically indicated.

Study End Points

Outcome measures were clinical response to CRT and long-term mortality. Patients were considered to be responders if they survived

to the 6 months follow-up visit with an improvement of at least 1 NYHA functional class. Echocardiographic data, including LVEF and left ventricular end-diastolic diameter (LVEDD), were also collected at baseline and reassessed at 6 months after the initiation of resynchronization therapy. Survival was assessed as the time from CRT implantation to all-cause mortality.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics software, version 23.0 (IBM, Armonk, NY) with the R software plug-in (The R Foundation, version 3.1.0) for propensity score matching. The Kolmogorov–Smirnov test was used to evaluate the normal distribution of continuous data. The χ^2 test was used to test for categorical variables and the 2-sample *t* test or the Mann–Whitney *U* test for continuous variables among patients groups.

The effects of baseline parameters on response rate were assessed by the χ^2 test and by a multivariate logistic regression model. To assess the effects of procedure type (ie, de novo versus upgrade) on survival, the Cox proportional hazards regression model was used. The statistical models were adjusted for potential baseline confounders, including sex, age, primary/secondary prevention indication, etiology of heart failure, atrial fibrillation, hypertension, dyslipidemia, diabetes mellitus, stroke/transient ischemic attack, peripheral arterial disease, chronic obstructive pulmonary disease, baseline NYHA class, baseline LVEF, presence of LBBB, QRS width, estimated glomerular filtration rate, and therapy with antiplatelet drugs, anticoagulants, β -blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, diuretics, statins, amiodarone, and digitalis, respectively. The univariate mortality risk assessment was also repeated among propensity score-matched patient groups. Patients receiving upgrade CRT were matched 1:1 with de novo subjects using the nearest neighbor matching method with a caliper of 0.2 by applying baseline characteristics listed above for the multivariate Cox regression.

Survival curves were constructed according to the Kaplan–Meier method and compared with the Cox proportional hazard model and the Wald test for the multivariate analysis. In addition, survival analysis was repeated for subgroups according to NYHA functional class (NYHA II versus NYHA III–IV) and to QRS width/morphology (>150 ms, LBBB). Two-sided *P* values <0.05 were considered statistically significant.

Results

Patients Characteristics

A total of 552 CRT-D recipients (Frankfurt 332, Bielefeld 103, and Budapest 117) were included in this analysis of whom 375 (68%) underwent a de novo implantation. A total of 177 patients (32%) had a previously implanted pacemaker or ICD system and underwent an upgrade procedure. Patients in the upgrade group were more often implanted for secondary prevention, suffered more often from atrial fibrillation, chronic kidney disease with a lower estimated glomerular filtration rate, diabetes mellitus, dyslipidemia, and had more often a non-LBBB wide QRS complex, and a lower LVEF. Furthermore, amiodarone and digitalis were more often prescribed for patients undergoing upgrade procedures (Table 1).

Response to CRT

Follow-up data on the NYHA status at 6 months were available in 96% of patients. After an upgrade procedure, 96 of 169 (57%) patients responded to CRT by improving their NYHA functional status by at least 1 class compared with

Table 1. Baseline Characteristics

	All (552)	De Novo (375)	Upgrade (177)	P Value
Male	427 (77.4%)	288 (76.8%)	139 (78.5%)	0.650
Age (Mean±SD)	67.1±11.1	66.5±11.3	68.3±10.4	0.141
Primary prevention	438 (79.3%)	335 (88.9%)	103 (58.2%)	<0.001*
Ischemic cardiomyopathy	298 (54.0%)	195 (51.7%)	103 (58.2%)	0.173
Atrial fibrillation	198 (35.9%)	124 (32.9%)	74 (41.8%)	0.046*
Chronic kidney disease	282 (51.1%)	165 (43.8%)	117 (66.1%)	<0.001*
Hypertension	381 (69.0%)	258 (68.8%)	123 (69.5%)	0.870
Diabetes mellitus	195 (35.3%)	117 (31.2%)	78 (44.1%)	0.003*
Dislipidemia	246 (44.6%)	155 (41.3%)	91 (51.4%)	0.026*
Stroke/TIA	69 (12.5%)	47 (12.5%)	22 (12.5%)	0.973
Peripheral artery disease	52 (9.4%)	36 (9.6%)	16 (9.0%)	0.833
Chronic obstructive pulmonary disease	67 (12.1%)	50 (13.3%)	17 (9.6%)	0.211
Left bundle branch block†	404 (74.8%)	287 (78.6%)	117 (66.9%)	0.003*
NYHA baseline (Mean±SD)	2.76±0.65	2.75±0.66	2.81±0.61	0.229
EF baseline (Mean±SD)‡	25.4±7.3	25.3±7.0	24.0±7.9	0.026*
QRS width baseline (Mean±SD)§	160.3±28.7	155.3±26.8	170.8±29.8	<0.001*
eGFR (Mean±SD)¶	62.1±52.6	65.4±59.2	55.1±34.1	<0.001*
Hemoglobin (Mean±SD)¶	13.2±2.0	13.2±2.0	13.4±1.8	0.334
Antiplatelet therapy	309 (56.0%)	213 (56.8%)	96 (54.2%)	0.571
Anticoagulation	272 (49.3%)	178 (47.5%)	94 (53.1%)	0.216
β-Blocker	533 (96.6%)	361 (96.3%)	172 (97.2%)	0.585
ACE-inhibitors/angiotensin receptor blockers	524 (94.9%)	358 (95.5%)	166 (93.8%)	0.401
Diuretics	497 (90.0%)	335 (89.3%)	162 (91.5%)	0.422
Mineralocorticoid receptor antagonists	397 (71.9%)	269 (71.7%)	128 (72.3%)	0.887
Statin	368 (66.7%)	250 (66.7%)	118 (66.7%)	1.000
Amiodarone	116 (21.0%)	56 (14.9%)	60 (33.9%)	<0.001*
Digitalis	213 (38.6%)	128 (34.1%)	85 (48.0%)	0.002*

ACE indicates angiotensin-converting enzyme.

†Available information for 540 patients.

‡Available information for 550 patients.

§Available information for 546 patients.

¶Available information for 539 patients.

¶Available information for 456 patients.

247 of 360 (69%) patients in the de novo group ($P=0.008$). The lower response rate among upgrade patients remained statistically significant in a multivariate logistic regression analysis ($P=0.021$; Figure 1). Pairwise echocardiographic

measurements (baseline and 6 months of follow-up) were available in 358 patients for LVEF (65%) and in 316 patients for LVEDD (57%). The echocardiographic changes were in line with the results of observed response rates based on the assessment of NYHA functional class. The improvement of LVEF and the decrease of LVEDD at 6 months were higher in the de novo group compared to the upgrade patients (Δ EF 6.7±9.4 versus 2.9±9.0, $P<0.001$; Δ LVEDD -3.5 ± 6.7 versus 0.0 ± 12.2 , $P=0.003$; Figure 2).

Mortality During Follow-Up

During a mean follow-up period of 37±28 months, survival was significantly worse among patients undergoing upgrade procedures compared to de novo CRT-D implantations (hazard ratio [HR], 1.65; 95% confidence interval [CI], 1.22–2.24; $P=0.001$; Table 2; Figure 3). After adjustment for potential confounders, all-cause mortality continued to be higher for patients in the upgrade group (adjusted HR, 1.68; 95% CI, 1.20–2.34; $P=0.002$; Table 2; Figure 3).

Using a 1:1 nearest neighbor matching protocol, a cohort of 121 pairs of patients undergoing de novo or upgrade CRT operation was assembled. Compared with prematched patients, those in the matched cohort showed completely balanced clinical parameters across a spectrum of the 26 baseline characteristics (Table I and Figure I in the Data Supplement). Also in this propensity-matched cohort, patients undergoing upgrade procedures had a higher mortality risk than patients undergoing de novo implantations (propensity-adjusted HR, 1.79; 95% CI, 1.08–2.95; $P=0.023$; Table 2; Figure 4).

Subgroup Analysis

Among patients with NYHA functional class II, there was no statistically significant difference in survival after de novo versus upgrade implantations (HR, 1.27; 95% CI, 0.61–2.65; $P=0.527$). However, in the subgroup of patients with NYHA class III–IV, the risk of all-cause mortality was higher in the upgrade group (HR, 1.67; 95% CI, 1.19–2.35; $P=0.003$; Figure 5). The response rate for de novo versus upgrade procedures was 67% versus 60% and 71% versus 62% in the subgroups of patients with LBBB or LBBB and QRS >150 ms ($P=NS$; Table II in the Data Supplement). The risk of death after upgrade CRT was increased in both the subgroups (Table II in the Data Supplement).

Discussion

Main Findings

The principal finding of this multicenter study comprising >550 CRT-D recipients is that survival after upgrade procedures was worse than after de novo implantations. All-cause mortality continued to be significantly higher for patients in the upgrade group after adjusting for potential confounders with multivariate Cox regression analysis and after applying propensity score matching. Similarly, clinical response was less favorable after an upgrade procedure compared with de novo implantations. To the best of our knowledge, this is one of the largest observational studies demonstrating worse

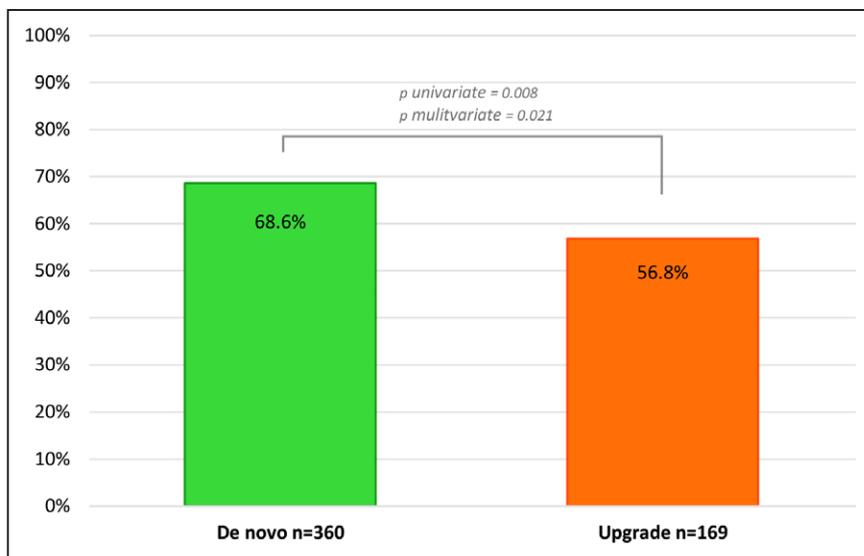


Figure 1. Clinical response rate at 6-month follow-up.

outcomes in patients undergoing a CRT upgrade compared to de novo CRT-D implantations.

Outcomes After Upgrade CRT

There is only sparse clinical evidence about clinical response to CRT after upgrade procedures. The few observational studies providing a head-to-head comparisons with de novo CRT implantations showed, in general, comparable results on various clinical parameters (eg, NYHA class, quality of life, 6-minute walk test, LVEF, end-systolic diameter, BNP levels, or hospitalizations).¹⁰⁻¹⁵

However, most of these studies were limited by their small patient sizes. In a recent European survey, similar improvements in NYHA functional class and similar reduction in QRS duration were found; however, more patients reported unchanged global assessment status in the upgrade group.⁹

Unfortunately, randomized, controlled data on the mortality of patients undergoing upgrade procedures are completely lacking. The available evidence mostly stems from the already mentioned survey report⁹ and from smaller retrospective analyses, which have yielded partially contradictory results. In the

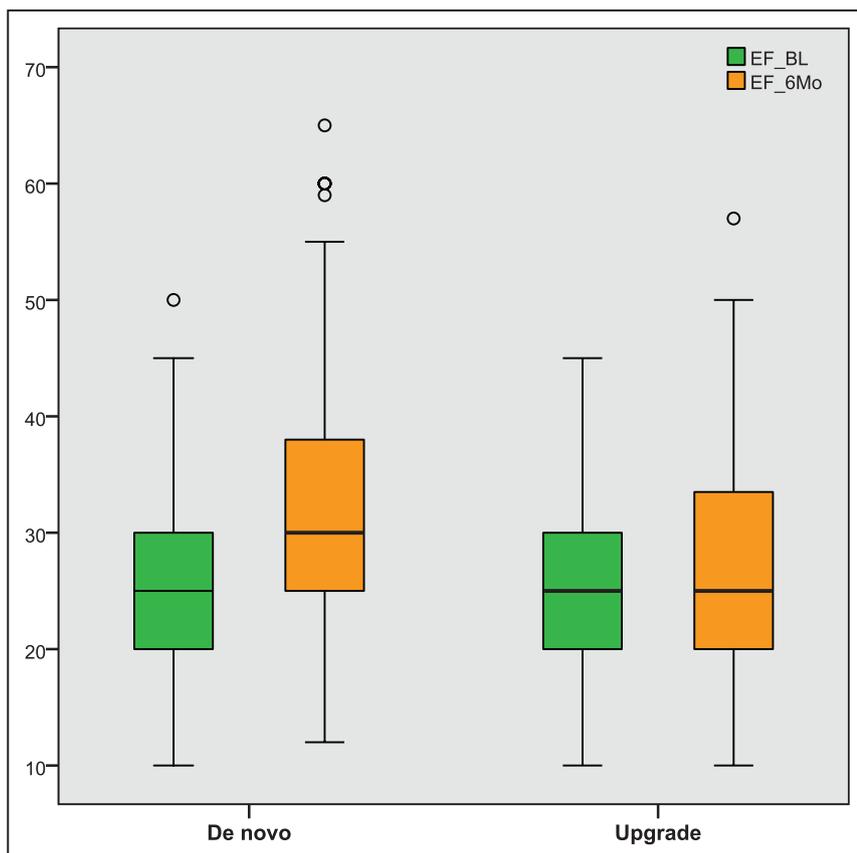


Figure 2. Left ventricular ejection fraction at baseline and at 6-month follow-up.

Table 2. Risk of Death by Implantation Type: De Novo vs Upgrade CRT

	Univariate Cohort (n=552)		Multivariate Cohort (n=501)*		Propensity-Matched Cohort (n=242)*	
	HR (CI 95%)	P Value	HR (CI 95%)	P Value	HR (CI 95%)	P Value
All-cause mortality	1.65 (1.22–2.24)	0.001	1.68 (1.20–2.34)	0.002	1.79 (1.08–2.95)	0.023

ACEIs indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LBBB, left bundle branch block; NYHA, New York Heart Association; TIA, transient ischemic attack.

*Models were adjusted for sex, age, primary prevention, pathogenesis, atrial fibrillation, hypertension, dyslipidemia, diabetes mellitus, stroke/TIA, peripheral artery disease, chronic obstructive pulmonary disease, baseline NYHA class, baseline EF, LBBB, QRS with at baseline, eGFR, NYHA response, and therapy with antiplatelet drugs, anticoagulants, β -blockers, ACEIs/ARBs, diuretics, mineralocorticoid receptor antagonists, statins, amiodarone, and digitalis.

largest single-center observational study,¹⁴ patients upgraded to CRT from previous RV-pacing tended to have better outcomes in terms of all-cause mortality (adjusted HR, 0.73; 95% CI, 0.53–1.01; $P=0.055$) compared with CRT patients without previous RV pacing. However, upgraded patients had smaller end-systolic and end-diastolic volumes at baseline; these different grades of remodeling may have influenced the response to CRT. Foley et al¹¹ described a similar long-term risk of mortality and morbidity between 336 patients undergoing de novo and 58 CRT recipients undergoing upgrade procedures from RV pacing. Of note, however, our study comprises more than 3 \times as many upgrade patients. No significant differences were found in a composite end point of 1-year device-related complication rate including death after 134 upgrade CRT operations compared with a randomly matched, equally sized sample of de novo

CRT implantations in a retrospective single-center analysis.¹⁶ However, when analyzed separately, 1-year mortality was more than doubled after upgrade procedures (19/113 versus 8/123).

The overall weak scientific evidence about the beneficial effects of a CRT upgrade has been recently emphasized by the 2016 European heart failure guidelines.¹⁷ These guidelines restrict the indication for upgrade CRT as a IIb class (level B) and do not indicate upgrade for patients with stable heart failure or with a QRS duration of <130 ms.

Factors Responsible for Reduced Benefit in Upgrade CRT Patients

In our series, patients in the upgrade group had more advanced heart disease and more comorbidities, which could explain the observed worse outcome. To account for these differences,

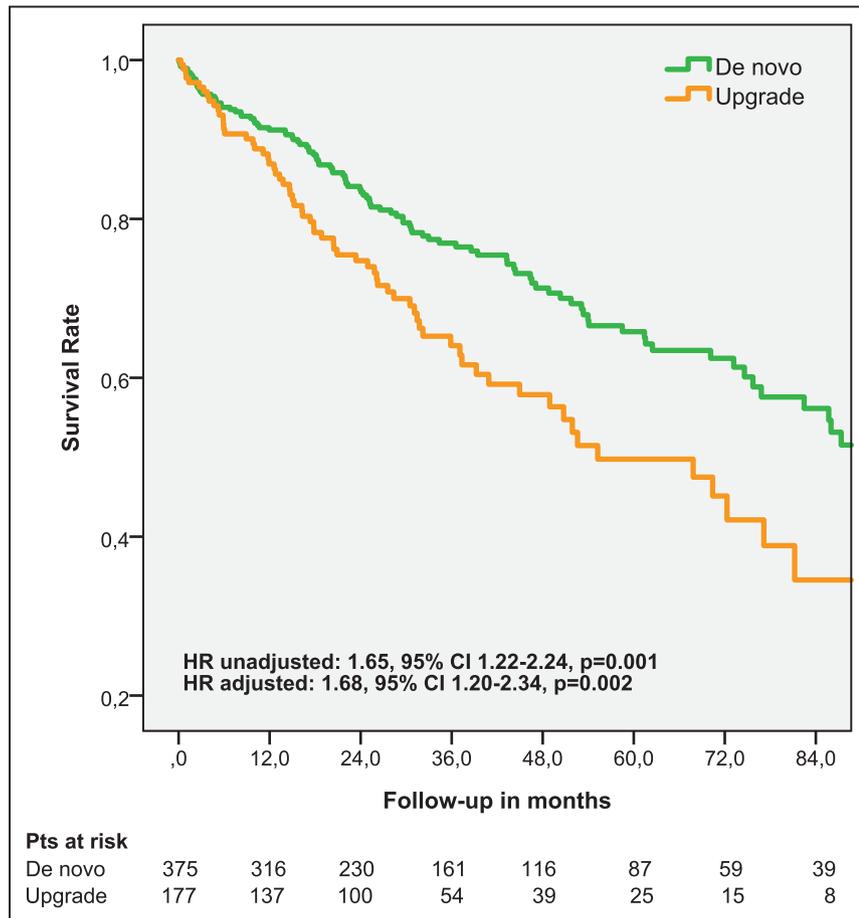


Figure 3. Kaplan–Meier curves for all-cause mortality by implantation type (all patients). CI indicates confidence interval; and HR, hazard ratio.

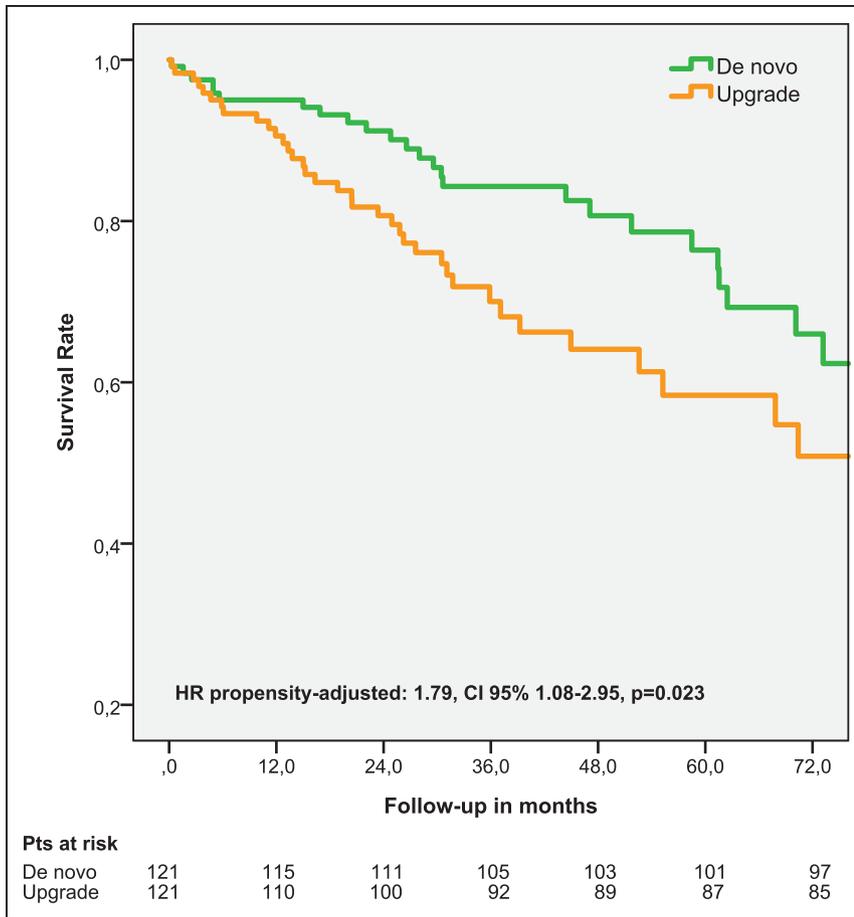


Figure 4. Kaplan–Meier curves for all-cause mortality by implantation type (propensity-matched patients). CI indicates confidence interval; and HR, hazard ratio.

we carefully adjusted the data for these baseline differences by various methods, including propensity score matching. In these adjusted analyses, findings consistent with the crude unadjusted analysis were observed.

Several considerations may help to explain our findings. The first one relates to the fact that resynchronization therapy may have been initiated too late in subjects who were upgraded from conventional pacemaker/ICD systems. It is conceivable that these patients were further advanced in their disease process and hence cardiac resynchronization had less chance to modify the risk for bad outcomes. This hypothesis is supported by the subgroup analysis according to NYHA functional class in which NYHA II patients showed similar mortality after both, de novo, and upgrade CRT. However, survival in NYHA III–IV patients was worse after upgrade procedures compared with de novo implantations. Chang et al¹⁸ showed recently that among patients who developed heart failure while being long-term paced from the RV only those responded to the CRT upgrade whose LVEF was $\geq 43.5\%$ at the time of deployment of RV pacing.

In addition, there is convincing evidence that only patients with typical LBBB respond well to CRT, but not those with RBBB or nonspecific intraventricular conduction disturbances.^{4–6} Accordingly, the worse clinical response pattern in patients with unspecific QRS abnormalities including those with a paced wide QRS complex may constitute another factor disfavoring CRT therapy. Our subgroup analysis according to QRS morphology and duration supports this notion.

Finally, CRT upgrade procedures may be associated with greater surgical risk than de novo procedures. Generally, reoperations could be more complex and carry a higher risk of acute complications, such as venous access issues, the risk of damage or extraction of old leads, higher infection rates, and longer procedure times. Notably, the incidence of postoperative complications was highest in patients undergoing the addition of a transvenous lead for replacement or upgrade in the REPLACE registry (Implantable Cardiac Pulse Generator Replacement).¹⁹ In the report from the Danish Pacemaker and ICD Register comprising 5918 consecutive patients, a system upgrade was also associated with a significantly higher complication risk (adjusted risk ratio, 1.3; 95% CI, 1.0–1.7; $P=0.02$).²⁰

Limitations

Because our study comprises a nonrandomized patient population, residual bias cannot be excluded. However, we aimed to minimize potential confounding by carefully adjusting our data to important patient characteristics possibly responsible for worse outcomes with 2 different statistical methods (ie, adjusted multivariate Cox regression and propensity score matching). It should be also noted that the matched propensity score analysis excludes 32% of the upgrade subjects, and thus addresses the question of comparability in a somewhat different population. Furthermore, echocardiographic follow-up parameters were not available for all patients.

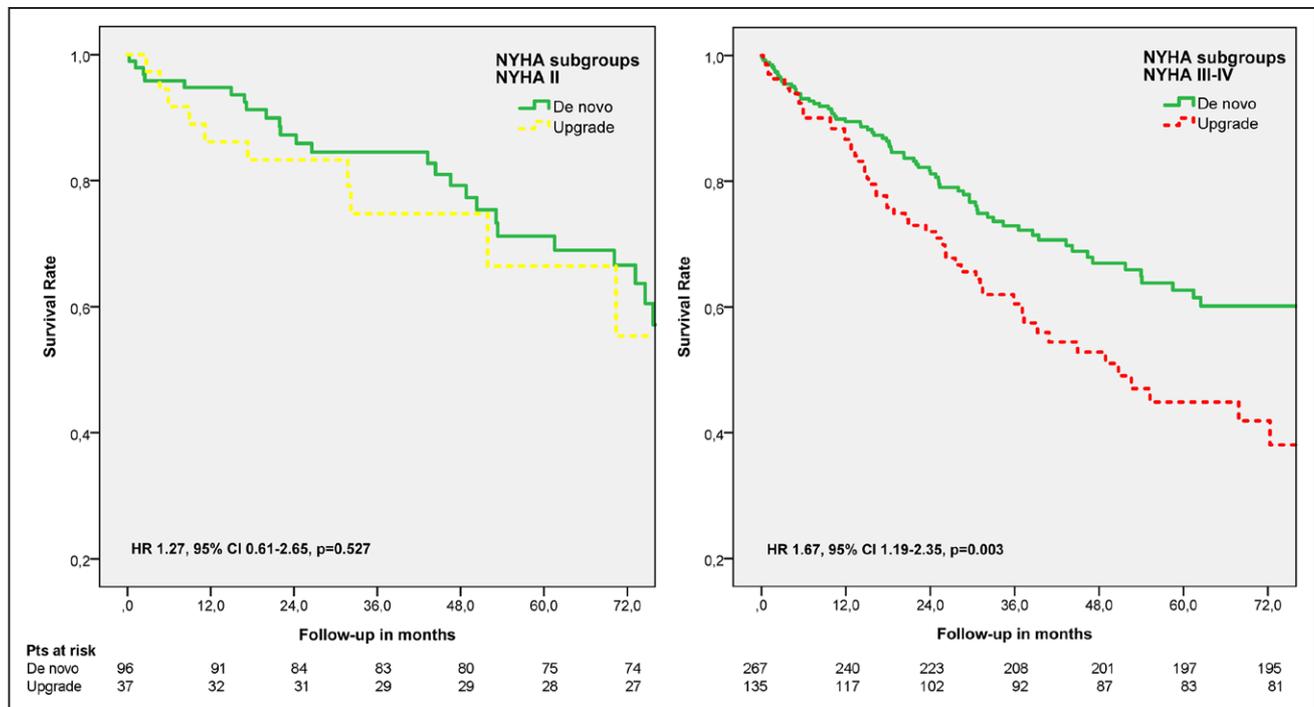


Figure 5. All-cause mortality in subgroups according to New York Heart Association (NYHA) functional class (Kaplan-Meier curves by implantation type). CI indicates confidence interval; and HR, hazard ratio.

Conclusions

Both clinical response and long-term outcome are less favorable in patients undergoing CRT-D upgrade compared to de novo implantation, even after careful adjustment for possible confounders. These findings warrant confirmation in prospective randomized trials, such as the ongoing BUDAPEST-CRT Upgrade Study.²¹ Until these results become available, our observations need to be considered when counseling individual patients on the need for a CRT upgrade.

Acknowledgments

We thank Prof Dr Eva Herrmann for her advice in the statistical part of the study. The technical support of Antje Steidl is greatly appreciated.

Disclosures

Dr Vamos reports lecture fees from Bayer and Pfizer and travel support from Bayer and SJM, outside the submitted work. Dr Linzbach received consulting fees from Pfizer, Daiichi Sankyo, Bayer und Boston Scientific, outside the submitted work. Dr Israel received consulting fees from Medtronic, and St. Jude Medical, lecture fees from Biotronik, Boston Scientific, Medtronic, Sorin/Livanova, and St. Jude Medical, and sponsored research from Boston Scientific, Medtronic, and Sorin/Livanova, outside the submitted work. Dr Duray received speakers' bureau from Medtronic, Biotronik, SJM, and Johnson&Johnson, outside the submitted work. Dr Hohnloser received consulting fees from Bayer, BI, Boston Scientific, BMS, Gilead, J&J, Medtronic, Pfizer, SJM, sanofi-aventis, and Cardiome, outside the submitted work. The other authors report no conflicts.

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Effects of Upgrade Versus De Novo Cardiac Resynchronization Therapy on Clinical Response and Long-Term Survival: Results from a Multicenter Study

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Circ Arrhythm Electrophysiol. 2017;10:e004471

doi: 10.1161/CIRCEP.116.004471

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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SUPPLEMENTAL MATERIAL

Supplementary Table 1 Baseline characteristics of propensity-matched patients

	All (242)	De novo (121)	Upgrade (121)	p-value
Male	182 (75.2%)	90 (74.4%)	92 (76.0%)	0.766
Age (Mean±SD)	67.5±10.8	67.4±11.4	67.6±10.2	0.898
Primary prevention	185 (76.4%)	93 (76.9%)	92 (76.0%)	0.880
Ischemic cardiomyopathy	136 (56.2%)	68 (56.2%)	68 (56.2%)	1.000
Atrial fibrillation	93 (38.4%)	46 (38.0%)	47 (38.8%)	0.895
Chronic kidney disease	140 (57.9%)	66 (54.5%)	74 (61.2%)	0.298
Hypertension	172 (71.1%)	88 (72.7%)	84 (69.4%)	0.571
Diabetes Mellitus	93 (38.4%)	45 (37.2%)	48 (39.7%)	0.692
Dislipidemia	120 (49.6%)	60 (49.6%)	60 (49.6%)	1.000
Stroke/TIA	25 (10.3%)	12 (9.9%)	13 (10.7%)	0.833
Peripheral artery disease	19 (7.9%)	10 (8.3%)	9 (7.4%)	0.811
Chronic obstructive pulmonary disease	21 (8.7%)	11 (9.1%)	10 (8.3%)	0.819
Left bundle branch block	178 (73.6%)	94 (77.7%)	84 (69.4%)	0.145
NYHA baseline (Mean±SD)	2.77±0.65	2.77±0.68	2.77±0.66	0.908
EF baseline (Mean±SD)	25.1±7.3	25.1±7.1	25.0±7.5	0.783
QRS width baseline (Mean±SD)	165.7±26.0	166.2±25.2	165.3±26.9	0.773
eGFR (Mean±SD)	58.8±31.0	59.0±22.6	58.6±37.7	0.229
Hemoglobin (Mean±SD)*	13.4±13.3	13.2±1.8	13.5±1.8	0.226
Antiplatelet therapy	132 (54.5%)	65 (53.7%)	67 (55.4%)	0.796
Anticoagulation	123 (50.8%)	63 (52.1%)	60 (49.6%)	0.700
β-Blocker	238 (98.3%)	119 (98.3%)	119 (98.3%)	1.000
ACE-Inhibitors/Angiotensin receptor blockers	231 (95.5%)	115 (95.0%)	116 (94.5%)	0.758
Diuretics	221 (91.3%)	112 (92.6%)	109 (90.1%)	0.493
Mineralocorticoid receptor antagonists	177 (73.1%)	92 (76.0%)	85 (70.2%)	0.310
Statin	159 (65.7%)	79 (65.3%)	80 (66.1%)	0.892
Amiodarone	52 (21.5%)	25 (20.7%)	27 (22.3%)	0.754
Digitalis	102 (42.1%)	51 (42.1%)	51 (42.1%)	1.000

*Available information for 191 patients

Supplementary Table 2 Response rate and risk of mortality in the subgroups of patients with LBBB or LBBB and QRS > 150ms

Subgroups	Response Rate			Mortality	
	De novo	Upgrade	p-value	HR (CI 95%)	p-value
Pts with LBBB	67% (185/275)	60% (68/113)	0.182	1.63 (1.12-2.37)	0.010
Pts with LBBB and QRS > 150ms	71% (117/166)	62% (45/73)	0.178	1.96 (1.25-3.08)	0.004

Supplementary Figure 1 Dotplot of standardized mean differences for 26 baseline characteristics between patients undergoing de novo or upgrade CRT implantation, before and after propensity score matching

