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Original Article

Mortality and Heart Failure After Upgrade to Cardiac Resynchronization Therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is effective in treating advanced heart failure (HF), but data describing benefits and long-term outcomes for upgrades from a preexisting device are limited. This study sought to compare long-term outcomes in de novo CRT implants with those eligible for CRT with a prior device.

Methods: This is a retrospective cohort study using data from a provincial registry (2002-2015). Patients were included if they had mild-moderate HF, left ventricular ejection fraction $\leq$ 35%, and QRS duration $\geq$ 130 ms. Patients were classified as de novo CRT or upgraded to CRT from a prior device. Outcomes were mortality and composite mortality and HF hospitalization.

Results: There were 342 patients included in the study. In a multivariate model, patients in the upgraded cohort (n = 233) had a higher 5-year mortality rate (adjusted hazard ratio, 2.86; 95% confidence interval, 1.59-5.15; $P = 0.0005$) compared with the de novo cohort (n = 109) and higher composite mortality and HF hospitalization (adjusted hazard ratio, 2.60; 95% confidence interval, 1.54-4.37; $P = 0.0003$).

Conclusions: Implantation of de novo CRTs was associated with lower mortality and HF hospitalization compared with upgraded CRTs from preexisting devices. It is unknown whether these differences are due to the timing of CRT implementation or other clinical factors. Further work in this area may be helpful to determine how to improve outcomes for these patients.

RÉSUMÉ

Contexte : La thérapie de resynchronisation cardiaque (TRC) est efficace pour traiter l'insuffisance cardiaque avancée, mais les données décrivant les bienfaits et les résultats à long terme de la mise à niveau d'un implant déjà en place sont limitées. La présente étude visait à comparer les résultats à long terme chez les patients recevant un implant de TRC *de novo* et chez ceux ayant déjà un implant qui sont admissibles à une TRC.

Méthodologie : Il s'agit d'une étude de cohorte rétrospective reposant sur les données issues d'un registre provincial (2002-2015). Les patients ont été inclus dans l'étude s'ils présentaient une insuffisance cardiaque légère ou modérée, une fraction d'éjection ventriculaire gauche $\leq$ 35 % et un intervalle QRS $\geq$ 130 ms. Les patients ont été classés dans le groupe TRC *de novo* ou dans le groupe TRC remplaçant un implant antérieur. Les paramètres d'évaluation étaient la mortalité et le critère regroupant la mortalité et l'hospitalisation pour insuffisance cardiaque.

Résultats : En tout, 342 patients ont été inclus dans l'étude. Après analyse selon un modèle multivarié, le taux de mortalité à 5 ans était plus élevé (rapport des risques instantanés [RRI] corrigé de 2,86; intervalle de confiance [IC] à 95 % de 1,59 à 5,15], $p = 0,0005$) dans la cohorte TRC remplaçant un implant antérieur (n = 233) que dans la cohorte TRC *de novo* (n = 109), tout comme le taux pour le critère regroupant la mortalité et l'hospitalisation pour insuffisance cardiaque (RRI corrigé de 2,60; IC à 95 % de 1,54 à 4,37], $p = 0,0003$).

Conclusions : L'implantation d'une TRC *de novo* était associée à un taux de mortalité et d'hospitalisation pour insuffisance cardiaque inférieur comparativement à l'implantation d'une TRC chez des patients ayant déjà un implant. On ne sait pas si ces différences sont attribuables au moment choisi pour l'implantation de la TRC ou à d'autres facteurs cliniques. D'autres études sur cette question pourraient être utiles afin de déterminer comment améliorer les résultats chez ces patients.

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Ethics Statement: Ethics approval was obtained from the Nova Scotia Health Authority research ethics board.

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See page 98 for disclosure information.

Randomized trials have demonstrated that among patients with mild to moderate heart failure (HF), reduced ejection fraction, and left bundle branch block, cardiac resynchronization therapy (CRT) significantly reduces mortality and HF

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hospitalization.[1-3] Despite the benefits of CRT, prior studies have mostly included patients with de novo CRT implants.[4] The **R**esynchronization in **A**mbulatory Heart **F**ailure **T**rial (RAFT) was one of the only trials that included patients with chronic ventricular pacing.[5] Patients with existing cardiac implantable electronic devices (CIEDs), such as implantable cardioverter defibrillators (ICDs) or pacemakers, may also become eligible for CRT subsequent to their initial implant. Recent guidelines have recommended evaluation of patients for possible upgrade to CRT at the time of system revision that may be for pulse generator change or other cause.[6,7] Patients with pacemakers who develop pacing-induced ventricular dyssynchrony and HF, and patients with ICDs and HF who subsequently develop a wide QRS represent the majority of patients eligible for upgrade to CRT platforms (CRT defibrillator [CRT-D] or CRT pacemaker).[8] Some centers have reported that 30% of CRT implant procedures represent upgrades from existing CIEDs.[9]

Data on long-term outcomes for patients with previous CIEDs who later become eligible for upgrade to CRT are scarce.[4,10] We sought to determine the risks and benefits of CRT upgrade in eligible patients compared with patients who undergo de novo CRT-D implantation.

Methods

Patient selection

This was a retrospective cohort study using a comprehensive provincial device registry to identify patients who were eligible for the study. The study was approved by the Nova Scotia Health Authority Research Ethics Board. The study identified all patients who underwent a CRT-D implantation or an upgrade to CRT-D from 2002 to 2015. Follow-up data were available for the entire population of patients with ICDs who reside in the province of Nova Scotia. Further details on the ICD registry have been described.[11]

Two patient cohorts were identified for comparison. The de novo CRT-D group included patients with New York Heart Association (NYHA) Class II/III HF, left ventricular ejection fraction (LVEF) $\leq 35\%$, and QRS duration ≥ 130 ms (or ≥ 200 ms if chronically paced) with a successful CRT-D implantation. The upgrade CRT-D group included those with the same criteria but had a preexisting ICD or pacemaker. Patients who underwent primary prevention ICD implantation for arrhythmogenic right ventricular cardiomyopathy, ion channelopathies, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, or other indications were excluded from this analysis, as were nonresidents of Nova Scotia. All therapies (shocks and antitachycardia pacing) from the implantable defibrillator were adjudicated for appropriateness by 2 cardiac electrophysiologists. Any disagreement between the 2 interpretations was resolved by review with a third electrophysiologist.

Outcomes

The main outcome measures were all-cause mortality and composite mortality and HF hospitalization. Mortality data were obtained through linkage with the provincial vital statistics registry.[11] HF hospitalization data were obtained through linkage with the Cardiovascular Health Nova Scotia database, a registry of all patients hospitalized in the province of Nova Scotia with the diagnosis of acute coronary syndrome or HF. Cases contained in the registry were identified using daily patient lists at all provincial institutions that provided inpatient hospital care starting in 2002. The diagnosis of HF was abstracted from the documented discharge diagnosis listed on the patient's hospital record. Trained data abstractors are employed by the Cardiovascular Health Nova Scotia to ensure reliability and accuracy of diagnostic coding. Details of this process have been published.[12] Secondary outcomes were early complications (occurring < 30 days from time of device implantation) and late complications (> 30 days). Early complications were defined as stroke, pneumothorax, subclavian vein thrombosis, sepsis/infection, hematoma, lead-related (eg, dislodgement, malfunction), myocardial perforation, pulmonary edema, cardiogenic shock, renal failure, or pericardial effusion. Late complications were defined as lead related (eg, dislodgement, malfunction), battery related, or infection/sepsis.

Follow-up

The follow-up schedule for these patients conformed to the guidelines for ICD follow-up with a blended in-clinic and remote monitoring system (ie, every 6 months).[13,14] ICD programming was left to the discretion of the electrophysiologist responsible for the patient. CRT pacing percentage was monitored at each follow-up with efforts to optimize pacing percentage, but no systematic optimization was performed. If patients were lost to follow-up, the last known date of follow-up was used, and data were censored thereafter.

Statistical analysis

The main outcomes were all-cause mortality and composite mortality and HF hospitalization; the secondary outcomes were early and late device-related complication. Baseline characteristics were summarized as mean $\pm$ standard deviation or prevalence (percentage), where appropriate. Categorical variables were compared using the chi-square test and continuous variables using the Student t test. By using the Kaplan–Meier method, overall mortality and a composite of mortality and HF hospitalization were compared between the de novo and upgrade cohorts. A multivariate analysis Cox proportional hazards model was performed to determine predictors of outcomes using variables known to influence risk of mortality and predict HF hospitalization,[15-17] including sex, age, creatinine, LVEF, diabetes mellitus, hypertension, peripheral vascular disease, β-blocker, use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, presence of paced QRS, and history of atrial fibrillation (AF). Hazard ratios were calculated for mortality and the composite. The log-rank test was used to test for significance between the cohorts. $P < 0.05$ was considered statistically significant. Model discrimination was assessed using Harrell's C-index[18] with R version 3.4.2. All other analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 342 patients included, and the median (interquartile range) follow-up for the entire cohort was 4.4

Table 1. Baseline characteristics: de novo vs upgrade to CRT-D

Variable	De Novo CRT-D (N = 233)	Upgrade to CRT-D (N = 109)	*P* value
Age, mean y (SD)	65.7 (9.3)	67.4 (9.9)	0.12
Creatinine, mean μmol/L (SD)	112.8 (40.7)	113.9 (38.1)	0.82
LVEF, mean % (SD)	23.9 (7.5)	24.6 (9.2)	0.52
QRS width, mean ms (SD)	154.8 (27.9)	171.5 (31.1)	< 0.0001
Left bundle branch block	134 (57.5)	18 (16.5)	
Right bundle branch block	13 (5.6)	3 (2.8)	
Nonspecific intraventricular block	39 (16.7)	9 (8.3)	
Paced rhythm	7 (3.0)	50 (45.9)	
Unknown	6 (2.6)	18 (16.5)	
Male, n (%)	190 (81.5)	87 (79.8)	0.66
Female, n (%)	42 (18)	22 (20.2)	0.66
NYHA III/IV, n (%)	136 (61.8)	38 (45.2)	0.01
Previous MI, n (%)	123 (52.8)	58 (53.2)	1
Previous PCI/CABG, n (%)	104 (44.6)	49 (45.1)	1
Previous pacemaker, n (%)	N/A	52 (47.7)	N/A
Previous ICD, n (%)	N/A	57 (52.3)	N/A
Diabetes, n (%)	114 (48.9)	32 (29.4)	0.0007
Hyperlipidemia, n (%)	151 (64.8)	68 (62.4)	0.72
Hypertension, n (%)	127 (54.5)	58 (53.2)	0.91
TIA/CVA, n (%)	25 (10.7)	18 (16.5)	0.16
History of AF, n (%)	69 (29.6)	46 (42.2)	0.03
COPD, n (%)	42 (18)	24 (22)	0.38
Peripheral vascular disease, n (%)	18 (7.7)	10 (9.2)	0.67
Current smoker	38 (16.3)	12 (11)	0.25
Beta-blocker, n (%)	220 (94.4)	102 (93.6)	0.81
ACEi/ARB, n (%)	211 (90.6)	95 (87.2)	0.35
Spironolactone, n (%)	74 (31.8)	28 (25.7)	0.31
Loop diuretic, n (%)	164 (70.4)	76 (69.7)	0.90
Oral anticoagulant, n (%)	72 (30.9)	49 (45)	0.02
Digoxin, n (%)	68 (29.2)	40 (36.7)	0.17
Amiodarone, n (%)	20 (8.6)	22 (20.2)	0.004
Other class III AAD, n (%)	2 (0.9)	3 (2.8)	0.33

AAD, antiarrhythmic drug (including sotalol or dofetilide); ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CVA, cerebrovascular accident; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not available; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischemic attack.

(2.3-6.5) years. De novo CRT-D implantation was performed in 233 patients (68.1%), and 109 patients (31.9%) were upgraded to CRT-D. The upgrade to the CRT-D cohort included 52 patients (47.7%) upgraded from previous pacemaker and 57 patients (52.3%) upgraded from previous ICD. Baseline characteristics for each group are presented in Table 1. Patients in the de novo CRT-D group had a higher prevalence of diabetes (48.9% vs 29.4%, $P = 0.0007$), lower prevalence of AF (29.6% vs 42.2%, $P = 0.03$), lower use of oral anticoagulants (30.9% vs 45%, $P = 0.02$), and lower use of amiodarone (8.6% vs 20.2%, $P = 0.004$) compared with the upgrade to the CRT-D cohort.

Outcomes

Increased mortality was found in the upgraded CRT-D group compared with the de novo group (unadjusted hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.04-2.49; $P = 0.033$) (Fig. 1). The 1- and 3-year survival rates in the de novo CRT-D patient population were 92.3% (95% CI, 88.0-95.1) and 78.6% (95% CI, 72.6-83.3), respectively, compared with 1- and 3-year survival rates of 87.2% (95% CI, 79.3-92.2) and 68.0% (95% CI, 58.2-76.0) in the upgrade to CRT-D patient population, respectively. On multivariate analysis, which included sex, age, creatinine, LVEF, diabetes mellitus, hypertension, peripheral vascular disease, β-blocker, use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, QRS width, and history of AF, mortality in the upgraded CRT-D group compared with the de novo group remained significantly higher (adjusted HR, 2.86; 95% CI, 1.59-5.15; $P = 0.0005$) (Table 2).

There were greater composite events of mortality and HF hospitalization in the upgraded CRT group compared with the de novo group (unadjusted HR, 1.50; 95% CI, 1.01-2.22; $P = 0.04$) (Fig. 2). On multivariate analysis, composite events of mortality and HF hospitalization remained significantly higher in the upgraded CRT group vs the de novo group (adjusted HR, 2.60; 95% CI, 1.54-4.37; $P = 0.0003$) (Table 3). The multivariate model discrimination was good for both mortality (c statistic = 0.76) and the composite of mortality and HF (c statistic = 0.72).

Device-related complications

Complications beyond 30 days postimplant occurred in 15 patients (6.4%) and 7 patients (6.4%) in the de novo CRT-D and upgraded groups, respectively (Table 4). The infection/erosion rate in the upgraded group was 2.7%, compared with 0.8% in the de novo group.

Discussion

In this cohort study, we found a reduction in mortality and in the composite end point of mortality and HF

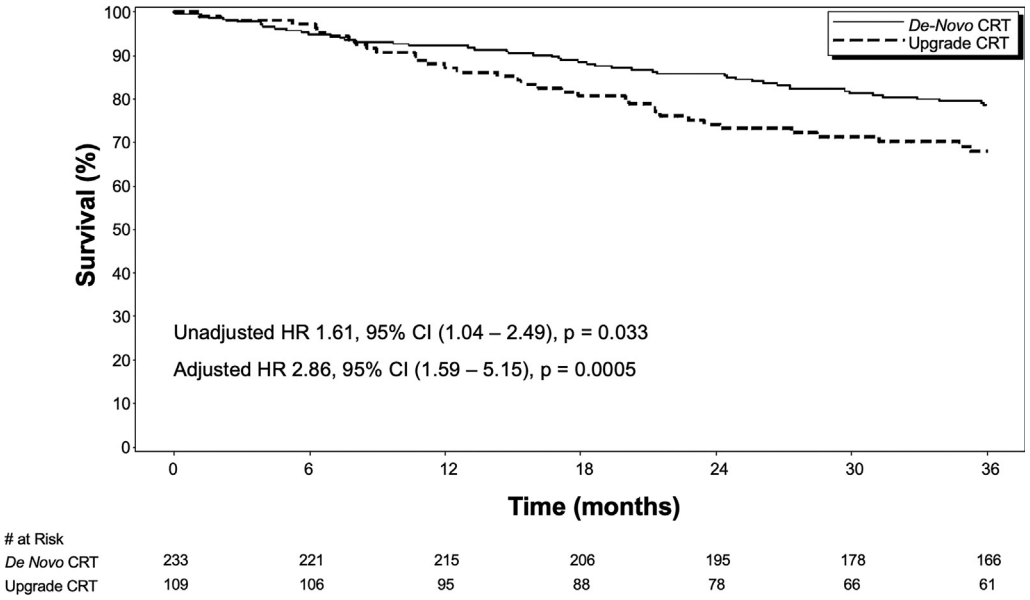

Figure 1. Mortality in the upgrade to cardiac resynchronization therapy defibrillator (CRT-D) vs de novo CRT-D cohorts. Mortality is depicted as a **solid line** in the de novo CRT-D cohort and as a **dashed line** in the upgrade to CRT-D cohort. CI, confidence interval.

hospitalization when comparing patients with de novo CRT-D implants with those who underwent an upgrade to CRT-D from preexisting CIEDs. The infection rate was low in both groups, but higher in the upgraded group, although this was not significant.

There are few studies that have examined long-term outcomes of mortality and HF hospitalization for patients who receive upgrades to CRT-D vs patients with de novo CRT-D implants. Several analyses have been conducted to date, but thus far, the available evidence has yielded conflicting results.[19-30] Bogale et al.[19] investigated 692 patients with upgrades to CRT/CRT-D and 1675 patients with de novo CRT/CRT-D, with follow-up of approximately 1 year, and did not find significant differences in survival ($P = 0.57$) between the 2 groups. Similar results were reported by a few other studies[21,23,24,29,30] with similarly short follow-up periods (ranging from reporting at 290 days to 4 years) or upgrades solely from pacemaker devices. Vamos et al.[28] conducted an observational prospective study with an average follow-up of 37 months and reported higher mortality in upgraded patients compared with patients with de novo CRT implants (HR, 1.79; 95% CI, 1.08-2.95; $P = 0.023$), whereas Cheung et al.[20] reported that CRT upgrades were independently associated with increased mortality (adjusted odds ratio, 1.91; 95% CI, 1.67-2.19; $P < 0.001$) compared with de novo CRT implants. Prior studies have reported similar HF rates between patients with de novo CRT vs CRT upgrades.[19,22,23] Our study demonstrated lower mortality and lower composite end point of mortality and HF hospitalization in patients receiving de novo CRT implants compared with those who received CRT upgrades.

Table 2. Multivariate analysis: Predictors of mortality in upgrade to CRT vs de novo CRT cohorts

Variable	Multivariate HR (95% CI)	*P* value
Upgrade vs de novo	2.86 (1.59-5.15)	0.0005
Male vs female	1.24 (0.60-2.56)	0.56
Age (per year)	1.00 (0.97-1.03)	0.97
Creatinine (per 10)	1.01 (1.00-1.02)	0.0003
LVEF	0.97 (0.94-1.01)	0.01
Diabetes	3.19 (1.89-5.40)	< 0.0001
Hypertension	0.89 (0.54-1.49)	0.66
Peripheral vascular disease	1.62 (0.83-3.17)	0.16
β-Blocker	1.45 (0.45-4.71)	0.54
ACEi/ARB	0.59 (0.29-1.19)	0.14
Presence of paced QRS	0.43 (0.20-0.89)	0.024
History of AF	1.60 (0.99-2.58)	0.05

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CI, confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Higher all-cause mortality and higher composite mortality and HF hospitalization in the upgraded cohort may be due to several factors. There was a higher proportion of patients with permanent AF. The RAFT study was composed of 229 patients (12.7%) with permanent AF and found no benefit to CRT in this subgroup.[5] Only one other study has examined the effect of CRT in patients with AF and found benefit in improved exercise tolerance.[31] A pooled analysis of 3 observational studies found an improvement in response in patients with atrioventricular junctional ablation.[32] The benefit of CRT in patients with permanent AF remains unclear. There is a current study that is attempting to address this question (**R**esynchronization/Defibrillation for **A**mbulatory Heart **F**ailure **T**rial in Patients With **Perm**anent **AF** [RAFT-PermAF], NCT01994252). In addition, there was a higher proportion of patients with prior right ventricular pacing in our study. The RAFT study included 135 patients (7.5%) with a paced QRS and found no benefit in this subgroup.[5] The Biventricular versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block (BLOCK HF) study was a randomized controlled trial comparing RV-only

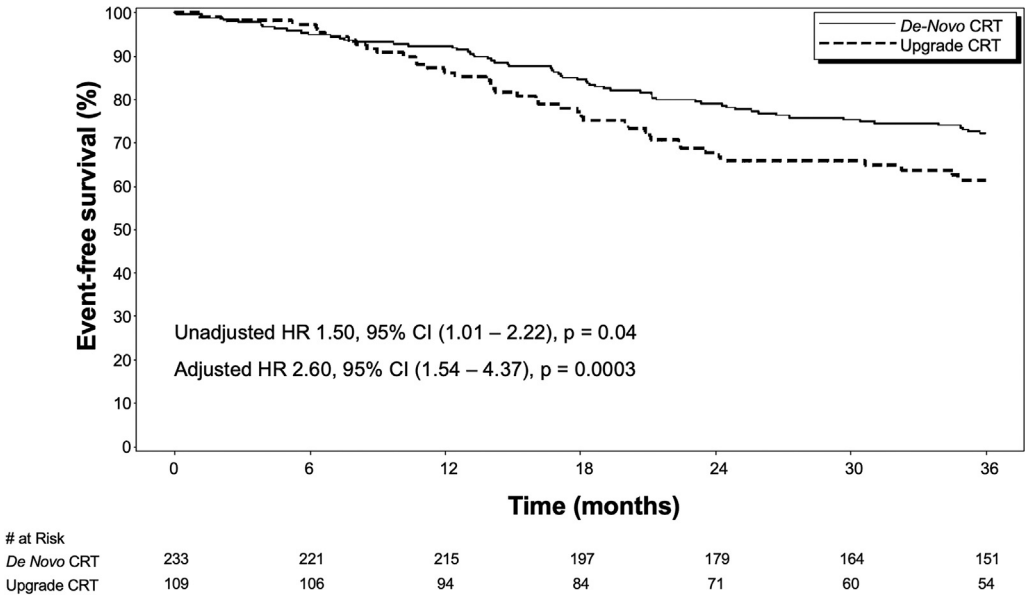

Figure 2. Composite mortality and heart failure (HF) hospitalization in the upgrade to CRT-D vs de novo CRT-D cohorts. Composite mortality and HF hospitalization is depicted as a **solid line** in the de novo CRT-D cohort and as a **dashed line** in the upgrade to CRT-D cohort. CI, confidence interval.

pacing with de novo CRT in patients with HF and atrioventricular block.[33] Patients with CRT had a 26% reduction in the composite outcome of death, urgent care visits for HF, or a $\geq$ 15% reduction in left ventricular end-systolic volume index, with a 22% reduction in death or hospitalization for HF, but all patients underwent de novo implants. Finally, it is possible that patients had already experienced significant progression in their disease process leading to worse outcomes despite CRT upgrades. For example, patients who initially received an ICD implant, because they did not meet CRT criteria, went on to develop widened QRS complexes and more severe HF (eg, NYHA III/IV) leading to a worse course of disease compared with de novo patients.[28,34] Of note, the presence of a paced QRS in our cohort was associated with improved outcomes in the multivariate analysis. This may be reflective of patients who were earlier in their HF course and were upgraded from pacemakers, rather than those who already had an ICD, had AF, or had progressive HF. Whether earlier intervention and upgrade to CRT would have altered outcomes in this population in unclear.

The use of His bundle pacing (HBP) in patients with significant conduction system disease requiring chronic pacing is being actively studied. Sharma et al.[35] performed a study using HBP as a rescue strategy in patients with failed left ventricular lead implant or CRT nonresponse. The success rate was 90% with an increase in LVEF from 30% $\pm$ 10% to 43% $\pm$ 13% ($P = 0.0001$) and improvement in NYHA functional class from 2.8 $\pm$ 0.5 to 1.8 $\pm$ 0.6 ($P = 0.0001$). Use of HBP may improve outcomes in those who are candidates for upgrade to CRT; further improvement in techniques to achieve HBP would be helpful in permitting this technique to be widely applicable.

Periprocedural complications associated with CRT implantation have been reported in a number of studies, with evidence in support of significantly higher complications with CRT upgrades,[20,36] similar complication rates between upgrades and de novo CRT implants,[19,27,37] and higher complications with de novo CRT implants.[4] However, in addition to demonstrating reduced acute complication rates for upgrades to CRT compared with de novo implants, Essebag et al.[4] also showed that the success rate for implanting

Table 3. Multivariate analysis: Predictors of composite events of mortality and heart failure hospitalization in upgrade to CRT vs de novo CRT cohorts

Variable	Multivariate HR (95% CI)	*P* value
Upgrade vs de novo	2.60 (1.54-4.37)	0.0003
Male vs female	1.70 (0.86-3.33)	0.13
Age (per year)	1.01 (0.98-1.03)	0.61
Creatinine (per 10)	1.01 (1.00-1.01)	0.002
LVEF	0.99 (0.96-1.02)	0.45
Diabetes	2.15 (1.37-3.36)	0.0008
Hypertension	0.91 (0.59-1.43)	0.69
Peripheral vascular disease	1.80 (1.01-3.23)	0.048
β-Blocker	1.58 (0.57-4.35)	0.38
ACEi/ARB	0.70 (0.37-1.32)	0.27
Presence of paced QRS	0.39 (0.20-0.76)	0.005
History of AF	1.52 (1.00-2.33)	0.05

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CI, confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Table 4. Device-related, late (> 30 days postimplant) complications

Variable	De novo CRT-D (N = 233)	Upgrade to CRT-D (N = 109)	*P* value
No. of patients, n (%)	15 (6.4%)	7 (6.4%)	1.00
No. of events	15	8	
Lead, n (%)	13 (5.6%)	5 (4.6%)	0.80
Battery erosion, n (%)	1 (0.4%)	1 (0.9%)	0.54
Infection or sepsis, n (%)	1 (0.4%)	2 (1.8%)	0.24

CRT-D, cardiac resynchronization therapy defibrillator.

de novo CRT devices was not significantly different from the rate of success for upgrades ($P = 0.402$). Our study demonstrated that procedural outcomes for patients undergoing device upgrades from ICD to CRT-Ds compared favorably with those receiving de novo implants.

Study limitations

The main limitations associated with this study were the retrospective and nonrandomized nature of patient selection, which carried selection and residual biases. There were also significant differences in baseline characteristics between the 2 cohorts, which may contribute, in part, to the observed outcomes. Last, we did not evaluate left ventricular remodeling, NYHA class, or functional capacity, which may have demonstrated some benefit for those patients in the upgraded group. The percentage of CRT pacing was not evaluated in follow-up in either group.

Conclusions

Compared with patients upgraded to CRT-D, patients with de novo CRT-D implantation had lower mortality and lower composite mortality and HF hospitalization, recognizing that there are limitations given the retrospective cohort design. It is unknown whether these observations are due to the timing of CRT implementation or other clinical factors such as the presence of AF. Further research in this area is required to optimize outcomes in these patients.

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