

Clinical outcomes after upgrading from pacemakers to cardiac resynchronization therapy

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Abstract

Background and aims: Right ventricular pacing may lead to heart failure (HF). Upgrades from pacemakers to cardiac resynchronization therapy (CRT) were excluded from most randomized, controlled trials. We sought to determine the long-term outcomes of upgrading from pacemakers to CRT with (CRT-D) or without (CRT-P) defibrillation in patients with no history of sustained ventricular arrhythmias.

Methods and results: In this observational study, clinical events were quantified in relation to the type of implant (*de novo* or upgrade) and device type at upgrade (CRT-P or CRT-D). Patients underwent CRT implantation ($n = 1,545$; 1,314 [85%] *de novo* implants and 231 [15%] upgrades) over a median of 4.6 years [interquartile range: 2.4–7.0]. In analyses of crude event rates, upgrades had a higher total mortality (adjusted hazard ratio [aHR]: 1.33; 95% confidence interval [CI] 0.10–1.61), a higher total mortality or HF hospitalization (aHR: 1.26; 95% CI 1.05–1.51), but similar mortality or hospitalization for major adverse cardiac events (MACEs, aHR: 1.15; 95% CI 0.96–1.38). No group differences emerged in any of these endpoints after propensity score matching. After inverse probability weighting in upgrades, total mortality (HR: 0.55; 95% CI 0.36–0.73), total mortality or HF hospitalization (HR: 0.56; 95% CI 0.34–0.79), and total mortality or hospitalization for MACEs (HR: 0.61; 95% CI 0.40–0.82) were lower after CRT-D than after CRT-P.

Conclusion: Upgrading from pacemakers to CRT was associated with a similar long-term risk of mortality and morbidity to *de novo* CRT. After upgrade, CRT-D was associated with a lower mortality than CRT-P.

KEYWORDS

cardiac resynchronization therapy, device upgrade, implantable cardioverter defibrillators, pacemakers

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) is a standard treatment for selected patients with heart failure, impaired left ventricular (LV) function, and a wide QRS complex.¹ Most randomized, controlled trials of CRT have excluded patients with previously implanted devices and, therefore, the randomized, controlled evidence base for CRT is limited to *de novo* CRT. Up to 27% of patients attending a typical pacemaker clinic have heart failure (HF).²

Right ventricular (RV) pacing is life-saving in patients with bradyarrhythmia, but it induces a pattern of ventricular activation akin to

a left bundle branch block. This causes (LV) mechanical dyssynchrony, which is now known to precipitate HF. The first clinical evidence for a detrimental effect of RV pacing emerged from randomized trials comparing the effects of atrial versus RV pacing in patients with sick sinus syndrome, in which up to 40% of patients developed HF with RV pacing.^{3,4} In the Dual Chamber and VVI Implantable Defibrillator (DAVID) study^{5,6} and the Mode Selection Trial (MOST),⁷ RV pacing was also associated with a higher risk of HF hospitalization.

Several studies have explored the acute and short-term effects of upgrading from RV pacing to CRT.^{8–13} We, as others, have shown that the symptomatic response^{12,14} and outcomes¹⁵ of upgrading to CRT

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are similar to *de novo* CRT. The 2012 ACCF/AHA/HRS (American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines/the Heart Rhythm Society) guideline¹⁶ recommended a CRT upgrade at generator replacement if LV function is severely impaired and the expected pacing requirement is $\geq 40\%$.¹⁷ An observational study of patients with implanted pacemakers or implantable cardioverter defibrillators (ICDs) upgraded to either CRT-pacemaker (CRT-P) or CRT-defibrillator (CRT-D)¹⁸ provided the evidence base for the 2016 European Society of Cardiology guideline recommendation to offer CRT upgrade to patients with HF. While upgrading was adopted in clinical practice even before such recommendations emerged,^{19,20} the clinical question remains as to whether CRT-D should be used in preference to CRT-P at the time of upgrading patients with pacemakers and without prior ventricular arrhythmias. In the present study, we have compared long-term outcomes of CRT-D and CRT-P, implanted either *de novo* or as an upgrade from pacemakers over a period of 16 years.

2 | METHODS

The study population consisted of patients undergoing a successful CRT device implantation for in the period from October 2000 to January 2016 at two centers (Queen Elizabeth Hospital and Good Hope Hospital, Birmingham, United Kingdom). Patients with a previous ICD implant or a sustained ventricular arrhythmia warranting upgrade to CRT-D were excluded. Some patients ($n = 394$) were included in a previous study.¹⁵ The present study increases the number of patients and the length of follow-up.

Device choice was influenced by the National Institute of Clinical Excellence guidelines, which in 2007 recommended CRT-P rather than CRT-D for patients with nonischemic cardiomyopathy and indications for CRT. With a subsequent guideline change in 2014 recommending CRT-D in nonischemic cardiomyopathy,²¹ the proportion of CRT-D recipients increased thereafter. The study was approved by the local Ethics Committee or the local Clinical Audit Departments, which waived the requirement for patient informed consent for audits of clinical care delivery and outcomes. The study conforms with the Declaration of Helsinki.

The diagnosis of HF was made on the basis of clinical features plus echocardiographic evidence of LV systolic dysfunction. The etiology of HF was based on the findings from clinical history (myocardial infarction, coronary revascularization) and/or investigation (e.g., cardiovascular magnetic resonance and nuclear imaging). Patients with hypertrophic or restrictive cardiomyopathy, primary valvular disease, sarcoidosis, amyloidosis, or myocarditis were excluded. Patients who were recruited to clinical trials were also excluded.

2.1 | Device therapy

Device implantation was undertaken using standard transvenous techniques under local anesthesia and intravenous sedation. After implantation, patients were followed-up in dedicated device therapy clinics. Device optimization using transmitral Doppler-directed optimization of atrioventricular delay using an iterative technique was undertaken up to 2013, when routine echocardiographic optimization

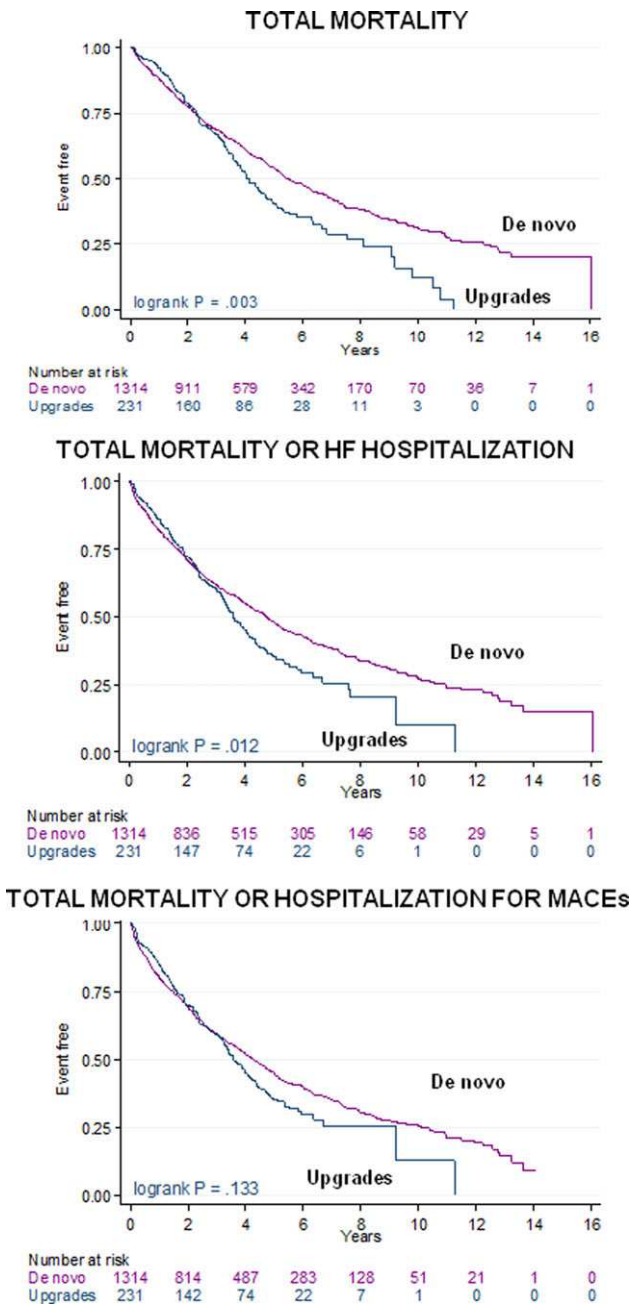


FIGURE 1 Primary and secondary endpoints in *de novo* implants and upgrades. Kaplan-Meier survival curves for clinical outcomes according to whether patients had a *de novo* implant or an upgrade. CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; HF = heart failure; MACE = major adverse cardiovascular events [Color figure can be viewed at wileyonlinelibrary.com]

was no longer deemed necessary on the basis of emerging evidence. Thereafter, optimization was only undertaken in symptomatic nonresponders. In patients in sinus rhythm, backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR with an interventricular delay of 0–20 ms (LV stimulation first). In patients with permanent atrial fibrillation, RV and LV leads were implanted and a CRT generator was used, plugging the atrial port and programming to a either VVIR or ventricular triggered modes, according to physician's discretion. Atrioventricular junction ablation was undertaken according to physicians' discretion.

TABLE 1 Baseline characteristics

	All	De novo	Upgrade	P*	Upgrade to CRT-D	Upgrade to CRT-P	P*
N	1,545	1,314	231		61	170	
Sex (male), n (%)	1,137 (73.59)	964 (73.36)	173 (74.89)	0.627	44 (72.13)	129 (75.88)	0.562
Age, years	72.1 ± 10.8	71.5 ± 10.8	75.5 ± 10.2	<0.001	71.9 ± 9.5	76.8 ± 10.2	0.001
≤59	203 (13.14)	185 (14.08)	18 (7.79)	<0.001	7 (11.48)	11 (6.47)	0.010
60–69	388 (25.11)	346 (26.33)	42 (18.18)		18 (29.51)	24 (14.12)	
70–79	586 (37.93)	498 (37.9)	88 (38.1)		22 (36.07)	66 (38.82)	
≥80	368 (23.82)	285 (21.69)	83 (35.93)		14 (22.95)	69 (40.59)	
NYHA class							
I	50 (3.32)	49 (3.83)	3 (0.01)	0.069	3 (1.69)	–	0.008
II	139 (9.24)	116 (9.07)	23 (10.18)		7 (11.86)	16 (9.58)	
III	1,091 (72.49)	925 (72.32)	166 (73.45)		49 (83.05)	117 (70.06)	
IV	225 (14.95)	189 (14.78)	36 (15.93)		2 (3.39)	34 (20.36)	
Device type, n (%)							
CRT-D	561 (36.31)	501 (38.13)	60 (25.97)	<0.001			
CRT-P	984 (63.69)	813 (61.87)	171 (74.03)				
Time to upgrade (days)	–	–	–	–	1,839 (697–2885)	1,396 (607–2433)	0.204
Etiology of cardiomyopathy, n (%)							
Ischemic	854 (55.28)	742 (56.47)	112 (48.48)	0.024	41 (67.21)	71 (41.76)	0.001
Nonischemic	691 (44.72)	572 (43.53)	119 (51.52)		20 (32.79)	99 (58.24)	
Comorbidities, n (%)							
Diabetes mellitus	340 (22.01)	293 (22.3)	47 (20.35)	0.509	11 (18.03)	36 (21.18)	0.601
Hypertension	441 (28.54)	374 (28.46)	67 (29)	0.867	12 (19.67)	55 (32.35)	0.061
CABG	289 (18.71)	240 (18.26)	49 (21.21)	0.289	16 (26.23)	33 (19.41)	0.264
ECG variables							
Sinus rhythm, n (%)	1,032 (66.84)	905 (68.93)	127 (54.98)	<0.001	40 (65.57)	87 (51.18)	0.053
Atrial fibrillation, n (%) [†]	512 (33.16)	408 (31.07)	104 (45.02)		21 (34.43)	83 (48.82)	
QRS morphology (LBBB), n (%)	1,235 (81.84)	1,008 (78.87)	227 (98.27)	<0.001	59 (96.72)	168 (98.82)	0.280
QRS duration (ms)	155.9 ± 23	153.5 ± 21.6	169.4 ± 25.7	<0.001	167.9 ± 24.7	169.9 ± 26.1	0.586
Medication, n (%)							
Loop diuretics	1,443 (93.4)	1,223 (93.07)	220 (95.24)	0.222	59 (96.72)	161 (94.71)	0.526
ACEIs / ARA	1,346 (87.12)	1,159 (88.2)	187 (80.95)	0.002	51 (83.61)	136 (80)	0.538
Beta-blockers	1,005 (65.05)	865 (65.83)	140 (60.61)	0.125	47 (77.05)	93 (54.71)	0.002
MRAs	656 (42.46)	582 (44.29)	74 (32.03)	0.001	24 (39.34)	50 (29.41)	0.154
LVEF (%)	24.4 ± 9.5	23.9 ± 9.4	24.4 ± 9.5	<0.001	25.7 ± 9.5	27 ± 10.1	0.399

Note: Variables are expressed as mean ± SD, unless indicated otherwise.

* refers to differences between the groups from ANOVA for continuous variables and from χ^2 tests for categorical variables.

[†] includes permanent, persistent, and paroxysmal atrial fibrillation (AF). ACEIs = angiotensin-converting enzyme inhibitors;

ARAs = angiotensin receptor blockers; CABG = coronary artery bypass grafting; CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; ECG = electrocardiogram; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association.

2.2 | Endpoints

The primary endpoint was total mortality, which included cardiac transplantation or implantation of a ventricular assist device. Secondary endpoints included: the composite endpoint of total mortality or HF hospitalization, and the composite endpoint of total mortality or unplanned hospitalization for major adverse cardiac events (MACEs), which included hospitalization for HF, myocardial infarction, acute coronary syndrome, and arrhythmia (ventricular tachycardia, ventricular fibrillation, and atrial fibrillation). Stroke and pulmonary embolism

were not considered as MACEs. In composite endpoints, the first event was used for censoring. Mortality data were collected through medical records and from interviews with patients' caregivers. Clinical events were collected every 6 months from the start of the study in 2000 by investigators who had access to patient clinical records, but no access to previously collected patient data or device-related data, which are kept separate from clinical records. Events were adjudicated by investigators at arbitrary intervals of 6 months using hospital records and death certificates.

TABLE 2 Event rates

	Total mortality			Total mortality or HF hospitalization			Total mortality or hospitalization for MACEs		
	Overall	CRT-D	CRT-P	Overall	CRT-D	CRT-P	Overall	CRT-D	CRT-P
Events (n)									
De novo	664	190	474	724	213	511	759	226	533
Upgrades	132	22	110	140	25	115	138	23	115
Incidence rates (%)									
De novo	12.3	10.1	13.4	14.7	12.3	16.0	16.2	13.5	17.7
Upgrades	16.4	9.4	19.2	19.2	11.1	22.8	19.3	10.1	23.5

Note: Data are expressed as number of events and annualized event rates (%). Abbreviations as in Table 1.

TABLE 3 Propensity score-matched samples for *de novo* implants and upgrades

	All	De novo	Upgrades	P*
N	420	210	210	
Sex (male), n (%)	315 (75)	158 (75.24)	157 (74.76)	0.910
Age, years	74.8 ± 10.1	74.6 ± 10	75 ± 10.3	0.663
≤59	34 (8.1)	16 (7.62)	18 (8.57)	0.553
60–69	84 (20)	43 (20.48)	41 (19.52)	
70–79	168 (40)	90 (42.86)	78 (37.14)	
≥80	134 (31.9)	61 (29.05)	73 (34.76)	
NYHA class				
I, II	50 (11.9)	27 (12.86)	23 (10.95)	0.681
III	302 (71.9)	147 (70)	155 (73.81)	
IV	68 (16.19)	36 (17.14)	32 (15.24)	
CRT-D, n (%)	114 (27.14)	57 (27.14)	57 (27.14)	1.000
Ischemic etiology, n (%)	210 (50)	106 (50.48)	104 (49.52)	0.845
ECG variables				
Atrial fibrillation, n (%)	185 (44.05)	94 (44.76)	91 (43.33)	0.768
QRS morphology (LBBB), n (%)	411 (97.86)	205 (97.62)	206 (98.1)	0.736
QRS duration (ms)	166.8 ± 23.6	167.2 ± 23.5	166.5 ± 23.8	0.759
Medication, n (%)				
ACEIs / ARA	348 (82.86)	171 (81.43)	177 (84.29)	0.437
MRA	145 (34.52)	73 (34.76)	72 (34.29)	0.918

Note: This shows the results of propensity score matching for *de novo* implants and upgrades. Note that the populations are well matched. Abbreviations as in Table 1.

TABLE 4 Propensity score matching and inverse probability weighting in upgrades to CRT-D versus upgrades to CRT-P

	Total mortality			Total mortality / HF hospitalization			Total mortality / Hospitalization for MACEs					
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P			
Propensity score matching (N = 116)	0.57	0.33	0.99	0.045	0.57	0.33	0.97	0.037	0.51	0.30	0.88	0.015
Inverse probability weighting (N = 226)	0.55	0.36	0.73	<0.001	0.56	0.34	0.79	<0.001	0.61	0.40	0.82	<0.001

Note: Results from propensity score matching and inverse probability weighting in upgraded patients, comparing CRT-D versus CRT-P. Results are expressed as hazard ratios (HR) and 95% confidence intervals (CI). HF = heart failure. Other abbreviations as in Table 1.

2.3 | Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Normality was tested using the Shapiro-Wilk test. Comparisons between normally distributed continuous variables were made using

analysis of variance, and categorical variables were analyzed using χ^2 tests. Kaplan-Meier curves and the log-rank test were used to assess observed cumulative survival. Cox proportional hazard models were used to assess relative risks. Proportionality hypotheses were verified

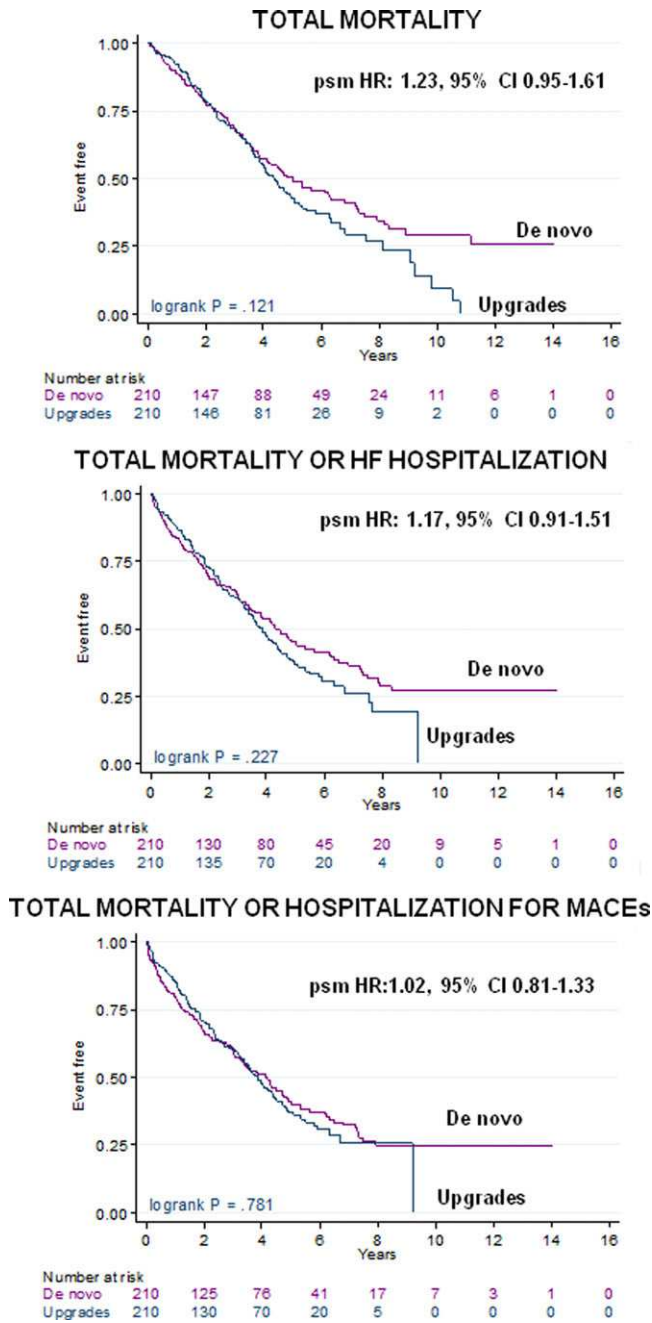


FIGURE 2 Primary and secondary endpoints in propensity-matched samples. Kaplan-Meier survival curves for clinical outcomes according whether patients had a *de novo* implant or an upgrade. CI = confidence interval; CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; HF = heart failure; MACE = major adverse cardiovascular events; psm HR = propensity score-matched hazard ratio [Color figure can be viewed at wileyonlinelibrary.com]

by visual examination of log (survival) graphs to ensure parallel slopes, and by examining Schoenfeld residuals. Variables with a $P < 0.10$ on univariable analyses were entered in multivariate models, and further backward elimination was applied for the final multivariate models. Statistical analyses were performed using Stata 14 (StataCorp, College Station, TX, USA). A two-tailed P -value of < 0.05 was considered statistically significant.

Propensity matching was undertaken for comparisons of *de novo* and for upgrades. Variables were selected if they differed significantly at baseline and if they emerged as predictors of total mortality. A 1:1 nearest-neighbor matching procedure within a caliper width of 0.01 was used. Each pair was used once and unpaired cases were excluded. The standardized difference was used to assess the balance between upgrades and *de novo* groups, and a difference of $< 10\%$ was accepted for matched cohorts.²² After matching, proportional hazards regression was used to compare survival outcomes in both groups. In the comparison between CRT-D and CRT-P upgrades, an inverse probability weighting approach was used, using all patients upgraded to CRT as reference.

3 | RESULTS

3.1 | Baseline characteristics in *de novo* implants and upgrades

Of 1,349 patients scheduled for *de novo* device implantation, a successful device implantation was achieved at the first attempt in 1,297 (96.1%) and at a second attempt in 17 (1.26%). Patients in whom a first unsuccessful implantation was not followed by other implantation attempts (30 [2.22%]) and those referred for surgical epicardial lead implantation (five [0.37%]) were excluded. Of 236 attempts at device upgrade, 228 (96.6%) were successful at the first attempt and three (1.27%) after a second attempt. One patient (0.42%) in whom a first unsuccessful upgrade was not followed by other attempts and one (0.42%) patient who died from HF within 2 days of device upgrade were excluded. After device upgrade attempts, no patients were referred for surgical epicardial lead implantation. After ≥ 1 successful implantation attempts, the total analytic population consisted of a total of 1,545 patients, 1,314 (85%) of whom were *de novo* implants and 231 (15%) were upgrades. The rate of failures from *de novo* device implantation or upgrades was uniformly distributed in the period 2001–2016 (data not shown).

As shown in Table 1, the *de novo* and upgrade groups were well matched for sex, New York Heart Association (NYHA) class, comorbidities, and uptake of loop diuretics and beta-blockers. Upgraded patients were on average 4 years older ($P < 0.001$) and were more likely to have atrial fibrillation ($P < 0.001$) and to receive CRT-P ($P < 0.001$). They had a higher LV ejection fraction (LVEF, $P < 0.001$) and were less likely to have ischemic cardiomyopathy ($P = 0.024$) and to have received angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARAs) ($P = 0.002$) and mineralocorticoid receptor antagonists (MRAs) ($P = 0.001$).

3.2 | Outcomes in *de novo* versus upgrade implants

Total mortality was 664/1,314 (50.5%; 12.3 per 100 person-years) in the *de novo* group and 132/231 (57.1%; 16.4 per 100 person-years) in the upgrade group over a maximum follow-up period of 16 years (median of 4.6 years, interquartile range [IQR]: 2.4–7.0; 4.7 years [IQR, 2.4–7.2] for *de novo* implants and 4.0 years [IQR: 2.0–5.7] for upgrades) (Table 2). In Kaplan-Meier survival analyses

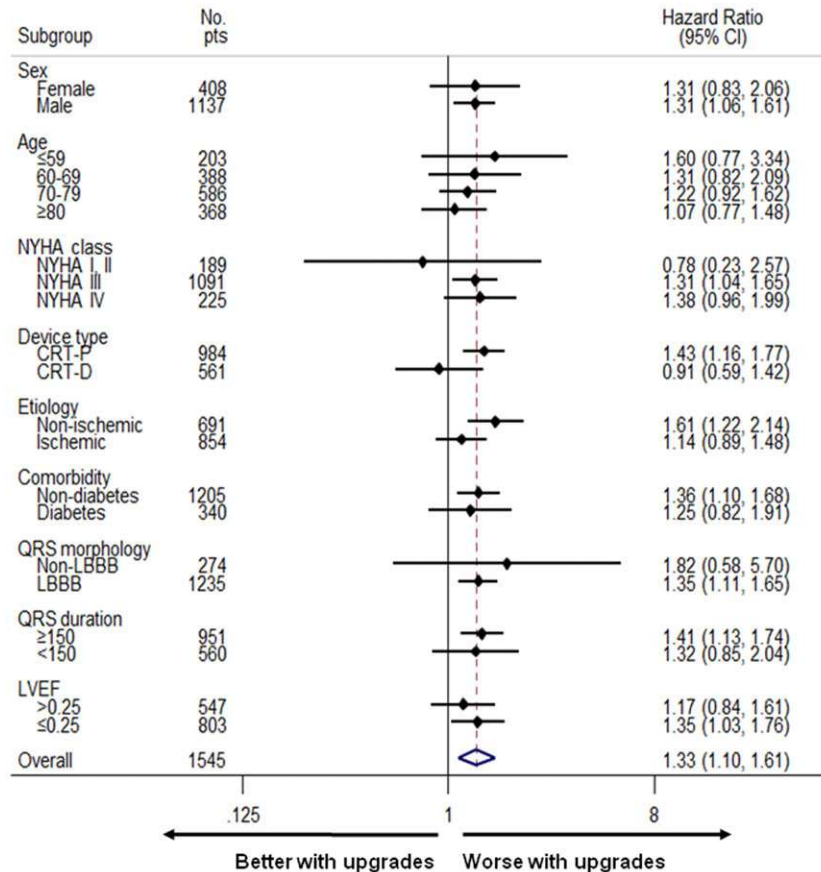


FIGURE 3 Subgroup analysis. Forest plot showing the risk of total mortality according to whether patients had a *de novo* implant or an upgrade. The horizontal lines indicate hazard ratios (HR) and 95% confidence intervals (95% CI) for total mortality for various subgroups. The vertical line represents the results for the entire analysis. CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association [Color figure can be viewed at wileyonlinelibrary.com]

(Figure 1), upgraded patients had a higher total mortality ($P = 0.003$) and total mortality or HF hospitalization ($P = 0.012$), but total mortality or hospitalization for MACEs was comparable. Results of univariate and multivariate Cox proportional hazards analyses are shown in the Online Appendix. In propensity score-matched samples (Table 3), total mortality (hazard ratio [HR]: 1.23, 95% confidence interval [CI] 0.95–1.61), total mortality or HF hospitalization (HR: 1.17, 95% CI 0.91–1.51), and total mortality or hospitalization for MACEs (HR: 1.02, 95% CI 0.81–1.33) were comparable (HRs are for upgrades compared to *de novo* implants). Multivariate Cox proportional hazards analyses also showed no differences in these endpoints (see Online Appendix). Similar findings emerged in analyses of propensity score-matched samples (Figure 2). As shown in subgroup analyses (Figure 3), total mortality after upgrades compared to *de novo* implants was significantly higher in men, NYHA class III, CRT-P, nonischemic cardiomyopathy, nondiabetic status, left bundle branch block, a QRS ≥ 150 ms, and a LVEF $\leq 25\%$.

3.3 | Baseline characteristics according to device upgrade type

Of the 231 upgraded patients, 61 (26.4%) were upgraded to primary prevention CRT-D and 170 (73.6%) to CRT-P. As shown in Table 1,

the groups were well matched for sex, comorbidities, atrial rhythm, QRS duration and morphology, LVEF, and uptake of ACEIs/ARAs and MRAs. Compared to CRT-P upgrade patients, CRT-D upgrade patients were 4.9 years younger ($P < 0.001$), had a better NYHA class (86.4% and 90.4% in NYHA class III or IV, respectively; $P = 0.008$), and were more likely to have ischemic cardiomyopathy ($P = 0.001$). In addition, CRT-D upgrade patients had a higher uptake of beta-blockers ($P = 0.002$).

3.4 | Outcomes according to device upgrade type

In Kaplan-Meier survival analyses (Figure 3), CRT-D upgrades had a lower total mortality ($P = 0.002$), total mortality or HF hospitalization ($P = 0.001$), and total mortality or hospitalization for MACEs ($P < 0.001$). We undertook a two-step procedure to correct variable imbalance. First, we undertook propensity score matching between *de novo* implants and upgrades (Table 3), using the variables either differed significantly at baseline or that emerged as predictors of primary endpoint, among which age emerged as a significant predictor. Second, we undertook both inverse probability weighting and propensity score matching between CRT-D and CRT-P upgrades in order to correct for age and other variables (Table 4). After inverse probability weighting (Figure 4), total mortality (HR: 0.55, 95% CI 0.36–0.73), total mortality

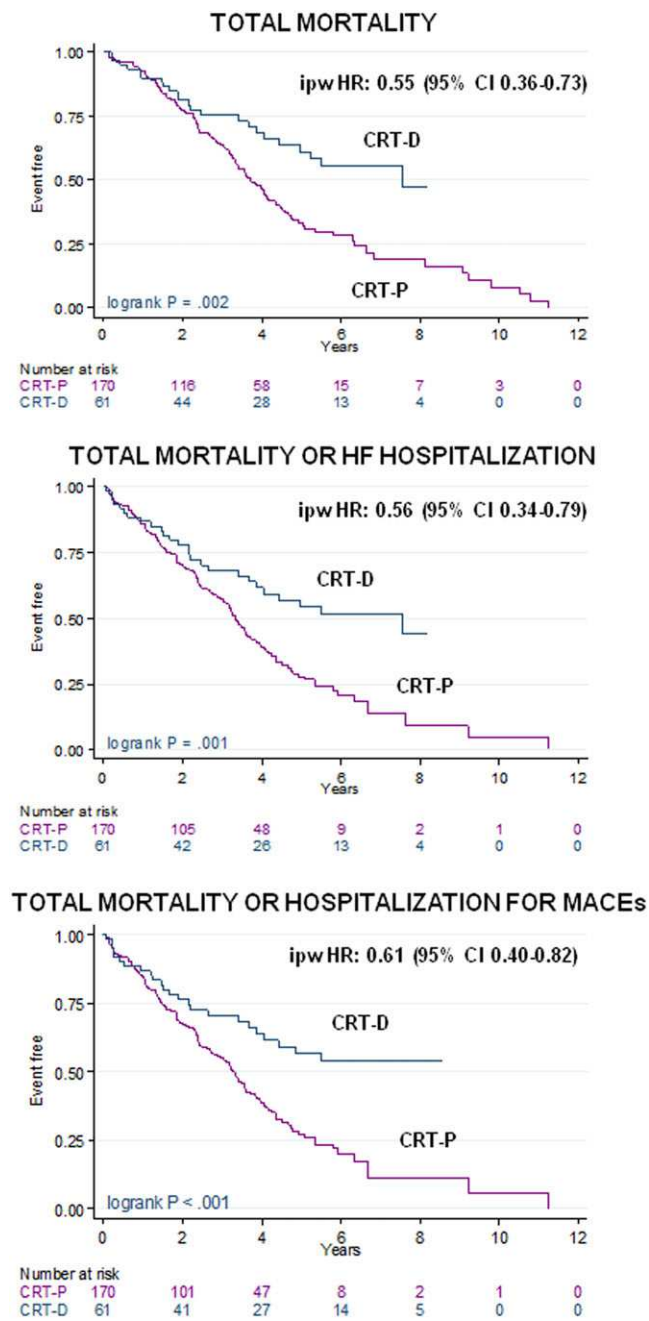


FIGURE 4 Primary and secondary endpoints according to device type at upgrade procedure. Kaplan-Meier survival curves for clinical outcomes according to device type at the time of upgrade. CI = confidence interval; CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; HF = heart failure; MACE = major adverse cardiovascular events; inverse probability weighting hazard ratio (ipw HR) for CRT-D compared with CRT-P upgrades [Color figure can be viewed at wileyonlinelibrary.com]

or HF hospitalization (HR: 0.56, 95% CI 0.34–0.79), and total mortality or hospitalization for MACEs (HR: 0.61, 95% CI 0.40–0.82) were lower after CRT-D than after CRT-P (all $P < 0.001$). The findings of multivariate Cox proportional hazards analyses and inverse probability weighting were similar. Cardiac mortality was lower in CRT-D upgrades (log-rank $P = 0.005$), but no differences in noncardiac mortality emerged (log-rank $P = 0.139$) (Figure 5).

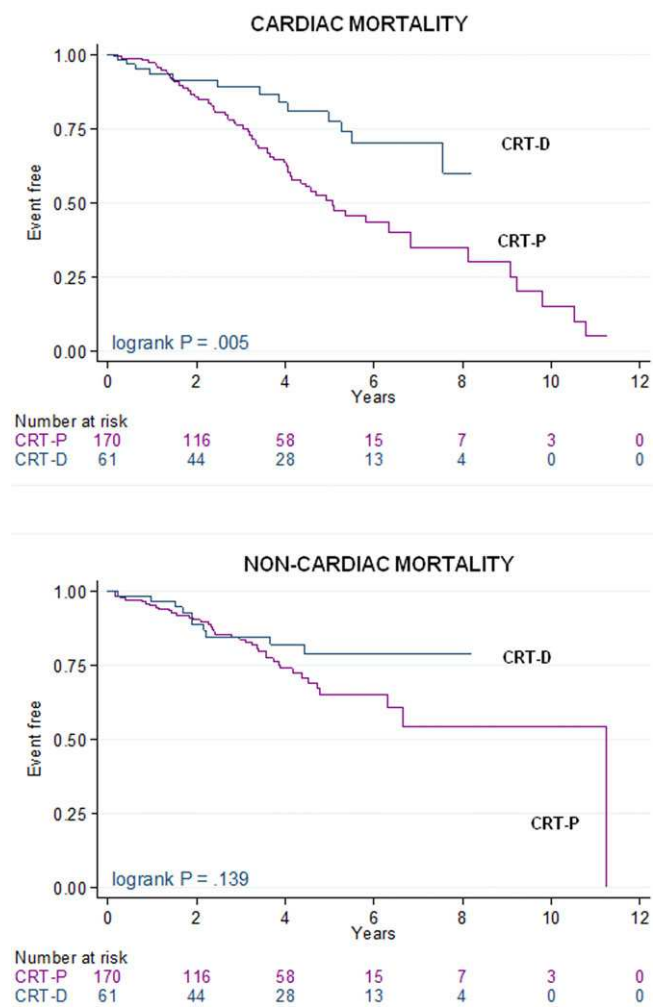


FIGURE 5 Cardiac and noncardiac mortality according to device type at upgrade procedure. Kaplan-Meier survival curves for cardiac and non-cardiac mortality according to device type at the time of upgrade. CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; HF = heart failure; MACE = major adverse cardiovascular events [Color figure can be viewed at wileyonlinelibrary.com]

To explore the effect of date of implantation on outcomes, we first included different year dummies on survival analyses and found that date of implantation did not emerge as a predictor of any of the endpoints. We also created a dichotomous variable, with year 2014 as the “cut-off.” In this analysis, no significant differences in outcomes emerged. Moreover, there was no interaction between date of upgrade and device type at the upgrade procedure (CRT-D vs CRT-P; data not shown).

4 | DISCUSSION

This is the largest study with the longest follow-up of patients undergoing upgrading from pacemakers to CRT-D or CRT-P in the context of primary prevention, i.e., patients with no history of sustained ventricular arrhythmias before the initial pacemaker implant or the CRT upgrade procedure. We found that, after covariate adjustment, the risk

of total mortality, total mortality or HF hospitalization, and total mortality or hospitalization for MACEs was similar in upgraded patients compared to patients undergoing *de novo* CRT implantation. Moreover, outcomes were consistently better after an upgrade to CRT-D rather than to CRT-P.

4.1 | *De novo* implants versus upgrades

Vamos et al. recently compared 375 *de novo* CRT-D implants and 177 CRT-D upgrade procedures.²³ Over a mean follow-up of 3.1 years, upgrades were associated with a higher mortality. Importantly, however, the patient population included upgrades from ICD to CRT-D and a large proportion of patients (42%) were upgraded to CRT-D for secondary prevention, compared to only 11.1% in the *de novo* group. Therefore, this study does not address upgrades in the context of primary prevention, but a heterogeneous population with a preexisting arrhythmic risk. In contrast, we found that after propensity score matching of “primary prevention” patients, outcomes were comparable after *de novo* implants and upgrades.

4.2 | CRT-D versus CRT-P upgrade

An argument for upgrading to CRT-P is that LV dysfunction in patients with pacemakers is likely to be due to RV pacing and that CRT should correct it, perhaps improving LV function to a degree that the LVEF improves above the cut-off of 35% that would obviate ICD therapy. For upgrading to CRT-D is that patients with pacemakers and a LVEF <35% fall under the indications for an ICD, with the exception that they already have a pacemaker. Pivotal to this question is whether CRT-D is superior to CRT-P in patients without prior ventricular arrhythmias. In a recent observational study of 199 pacemaker patients with no history of sustained ventricular arrhythmias, Barra et al. included 104 upgrades to CRT-P and 95 upgrades to CRT-D. Over a mean follow-up of 5.5 years, three of 104 (2.9%) patients in the CRT-P arm had a primary arrhythmic death (6.2 sudden arrhythmic deaths per 1,000 patient-years). The authors concluded that patients with pacing-induced cardiomyopathy and no prior ventricular arrhythmias who are upgraded to CRT may not derive any significant benefit from the addition of a defibrillator.²⁴ In contrast, we found that CRT-D upgrade was consistently superior to CRT-P upgrades with respect to the three main endpoints, even after inverse probability weighting. In addition, analysis of cause of death showed that this was predominantly due to a lower cardiac rather than noncardiac death. Our findings have emerged in the context of the ongoing BUDAPEST CRT trial,²⁵ which will compare upgrading from pacemakers to ICD or CRT-D, but not from pacemakers to CRT-P or CRT-D. Currently, there are no planned trials addressing whether CRT-D is superior to CRT-P at the time of upgrading from pacemakers in the context of primary prevention.

4.3 | Limitations

This is nonrandomized and observational study and, therefore, our findings should be interpreted with caution. The groups were significantly unbalanced. In particular, there was a specific bias toward CRT-

P in nonischemic cardiomyopathy and CRT-D in ischemic cardiomyopathy. This is a known bias. As this study was not randomized, there will also be multiple unknown biases which may influence survival and other outcomes. Unfortunately, LV function was not systematically coded prior to implantation of conventional pacemakers. Given that some patients underwent the original pacemaker implantation before the advent of CRT, it is possible that, in contrast to our current practice, a proportion may not have had an echocardiogram. Some patients may have had LV dysfunction and/or HF at the time of pacemaker implantation. In addition, the serial uptake of RV pacing was not systematically collected and reduction of RV pacing was not systematically attempted, as this study precedes the development of appropriate algorithms. In addition, programming and changes thereof throughout the follow-up period, which were not systematically addressed, could also impact on outcomes. The lack of systematic collection of therapies (antitachycardia pacing and shocks) delivered is further limitation.

5 | CONCLUSIONS

We have found that in patients with HF and preexisting pacemakers, upgrading to CRT is associated with a similar long-term risk of mortality and HF hospitalization to patients undergoing *de novo* CRT. In upgraded patients, CRT-D was associated with lower mortality than CRT-P.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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