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RESEARCH ARTICLE

Long-term outcome after upgrade to cardiac resynchronization therapy: A propensity score-matched analysis

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Aim

Cardiac resynchronization therapy (CRT) is a cornerstone in the management of chronic heart failure in patients with a broad or paced QRS. However, data on long-term outcome after upgrade to CRT are scarce.

Methods and results

This international, multicentre retrospective registry included 2275 patients who underwent a *de novo* or upgrade CRT implantation with a mean follow-up of 3.6 ± 2.7 years. The primary composite endpoint included all-cause mortality, heart transplantation, or ventricular assist device implantation. The secondary endpoint was first heart failure admission. Multivariable Cox regression and propensity score matching (PSM) analyses were performed. Patients who underwent CRT upgrade ($n = 605$, 26.6%) were less likely female (19.7% vs. 28.8%, $p < 0.001$), more often had ischeemic cardiomyopathy (49.8% vs. 40.2%, $p < 0.001$), and had worse renal function (median estimated glomerular filtration rate 50.3 ml/min/1.73 m^2 [35.8–69.5] vs. 59.9 ml/min/1.73 m^2 [43.0–76.5], $p < 0.001$). The incidence rate of the composite endpoint was 10.8%/year after CRT upgrade versus 7.1%/year for *de novo* implantations ($p < 0.001$). PSM for the primary endpoint resulted in 488 pairs. After propensity score matching, upgrade to CRT was associated with a higher chance to reach the composite endpoint (multivariable hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.08–1.70), for both upgrade from pacemaker (multivariable HR 1.33, 95% CI 1.03–1.70) and implantable cardioverter-defibrillator (ICD) (multivariable HR 1.40, 95% CI 1.01–1.95). PSM for the secondary endpoint resulted in 277 pairs. After PSM, upgrade to CRT was associated with a higher chance for heart failure admission (HR 1.74, 95% CI 1.26–2.41).

Conclusion

In this retrospective analysis, the outcome of patients who underwent upgrades to CRT differed significantly from patients who underwent *de novo* CRT implantation, particularly for upgrades from ICD. Importantly, this difference in outcome does not imply a causal relation between therapy and outcome but rather a difference between two different patient populations.

Keywords

Cardiac resynchronization therapy • Upgrade • Heart failure • Pacemaker • Implantable cardioverter-defibrillator

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Introduction

In the past decades cardiac resynchronization therapy (CRT), with or without implantable cardioverter-defibrillator (ICD) function, has become a cornerstone in the treatment of heart failure in patients with a broad or paced QRS.[1,2] The indications for *de novo* CRT are well-defined and supported by landmark randomized clinical trials.[3] However, despite accounting for approximately 30% of CRT procedures,[4] data on the outcome of upgrade to CRT in patients with a pre-existing pacemaker or ICD are limited and conflicting.[5–8] In a meta-analysis, which predominantly included small single-centre studies with a follow-up of ≤1 year, all-cause mortality and clinical benefit were comparable between *de novo* and upgrades to CRT.[7] However, in a prospective, multicentre cohort study with a mean follow-up of 3 years, all-cause mortality and clinical response rates were significantly less favourable in patients who underwent upgrade to CRT from ICD when compared to *de novo* CRT.[8]

Therefore, we aimed to study the long-term outcome of patients who underwent an upgrade to CRT in a large, multicentre CRT registry using propensity score-matched analysis.

Methods

Study population

All patients with ischaemic or non-ischaemic cardiomyopathy aged ≥18 years who underwent *de novo* CRT implantation or upgrade from a pacemaker or ICD to CRT in three tertiary care centres were included in a retrospective registry. The participating centres were the University Hospitals Leuven (Leuven, Belgium), Ziekenhuis Oost-Limburg (Genk, Belgium), and the University Hospital Zurich (Zurich, Switzerland). CRT indications were in accordance with the European Society of Cardiology guidelines at the time of implantation or upgrade.[1,9] Clinical follow-up and optimization of guideline-directed medical therapy and CRT programming were left to institutional preferences. The study was approved by the ethics committee of each individual institution (Leuven: S64276, Genk: b371201627103, Zürich-KEK-ZH-NR: 2011-0304). The need for a written informed consent was waived due to the retrospective nature of the study.

Retrospective registries

Demographics, clinical characteristics, baseline medical therapy, as well as biochemical, electrocardiographic, and echocardiographic data before CRT implantation or upgrade were collected retrospectively from the electronic medical records. Ischaemic cardiomyopathy was defined as patients where the underlying aetiology of the cardiomyopathy was most likely due to coronary artery disease. Overall, procedural dates ranged from 30 November 2000 to 31 December 2019, and inclusion dates and follow-up differed between centres. Left ventricular ejection fraction (LVEF) prior to CRT implantation or upgrade was obtained from cardiac magnetic resonance imaging or two-dimensional echocardiography (modified Simpson's biplane method in the apical two- and four-chamber view or visual assessment, whichever was available). Registries were merged under supervision of two investigators (B.V. and S.T.). For this study only variables in common were used for further analysis.

Endpoints

The primary endpoint was a composite of all-cause mortality, heart transplantation or implantation of a ventricular assist device. The secondary endpoint was first hospital admission for heart failure. Individual endpoint events were collected with the respective dates. Patients were included in the analysis until the last available follow-up. In case of heart transplantation or ventricular assist device implantation, the date of last follow-up was the date of transplantation or ventricular assist device implantation. Of note, patients from Ziekenhuis Oost-Limburg were referred to the University Hospitals Leuven for transplantation or ventricular assist device implantation. Heart failure admission was defined as a hospital admission lasting for more than 24 h, with signs or symptoms of congestion necessitating an increase of the dose of loop diuretics. No data on heart failure admission were available for patients from Ziekenhuis Oost-Limburg (Genk, Belgium).

Statistical analysis

Continuous variables were presented as median and interquartile range, as all continuous variables showed non-normal distribution using Kolmogorov–Smirnov testing for normality. Categorical variables were presented as number and percentage. Comparison of parameters between groups was performed using Mann–Whitney U testing and χ^2 testing. Incidence rates were calculated using Kaplan–Meier analysis and groups were compared with log-rank testing. Univariable and multivariable Cox proportional hazard regression modelling was performed for the time-to-event endpoints. All variables with a $p < 0.100$ in univariable regression were included in a stepwise multivariable model with forward parameter selection (entry $p < 0.050$). The final models were, if applicable, assessed using proportional hazard plots and the Schoenfeld residuals test for the proportional hazard assumptions, and covariance matrices for multicollinearity. In case of violation of the proportional hazard assumptions, stratification was applied. Final models are available in online supplementary material. To investigate the effect of upgrades on the endpoints, a 1:1 propensity score matched analysis was performed with 13 relevant clinical variables using the nearest neighbour method without replacement, using common support and a caliper set at 0.001. Given the difference in data availability, separate propensity score matching was performed for the primary and secondary endpoint. The quality of the matched samples was assessed using a before–after standardized mean difference plot with correction for sample size (Cohen's d) and a threshold of 0.1 for acceptable imbalance. After propensity score matching the same final model was repeated for each endpoint, including the assessment of the proportional hazard assumptions. Missing values were handled by list wise deletion. Statistical analyses were performed using Stata (StataCorp LLC, College Station, TX, USA) and GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA, USA).

Results

Demographics and clinical characteristics

A total of 2275 patients were included in the registry. Baseline data and comparison between *de novo* implantations and upgrades are shown in *Table 1*. Overall, the median age was 70.3 years (61.8–76.8), 26.4% were female and 42.8% had ischaemic cardiomyopathy. Upgrade to CRT was performed in 605 patients

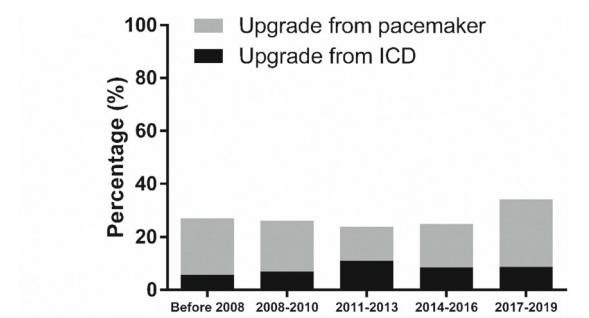
Table 1 Baseline demographics and clinical characteristics

Variable	Availability	All patients	*De novo* implantation	Upgrade	*p*-value
Patients, *n*	2275	2275 (100%)	1670 (73.4%)	605 (26.6%)	
Age at implant (years)	2274	70.3 (61.8–76.8)	70.2 (61.9–76.7)	70.6 (61.8–76.8)	0.671
Female sex	2262	596 (26.4%)	477 (28.8%)	119 (19.7%)	<0.001
CRT-D	2271	1452 (63.9%)	1047 (62.8%)	405 (67.1%)	0.063
Epicardial LV lead	2269	136 (6.0%)	66 (4.0%)	55 (9.2%)	<0.001
ICMP	2249	962 (42.8%)	663 (40.2%)	299 (49.8%)	<0.001
Arterial hypertension	2258	1535 (68.0%)	1136 (68.6%)	399 (66.2%)	0.265
Dyslipidaemia	2251	1451 (64.5%)	1049 (63.5%)	402 (67.0%)	0.129
Stroke	2248	229 (10.2%)	156 (9.5%)	73 (12.2%)	0.064
Diabetes mellitus	2261	602 (26.6%)	451 (27.2%)	151 (25.0%)	0.278
LVEF (%)	2227	27.0 (21.0–34.0)	27.0 (21.0–34.0)	28.0 (20.0–34.3)	0.913
≤35%		1890 (84.9%)	1400 (85.6%)	490 (82.9%)	0.019
35–50%		292 (13.1%)	198 (12.1%)	94 (15.9%)	
>50%		45 (2.0%)	38 (2.3%)	7 (1.2%)	
eGFR (ml/min/1.73 m^2)	2217	57.8 (41.2–74.7)	59.9 (43.0–76.5)	50.3 (35.8–69.5)	<0.001
CKD 1–2		1043 (47.1%)	810 (49.8%)	233 (39.5%)	<0.001
CKD 3a		489 (22.1%)	371 (22.8%)	118 (20.0%)	
CKD 3b		401 (18.1%)	260 (16.0%)	141 (23.9%)	
CKD 4–5		284 (12.8%)	186 (11.4%)	98 (16.6%)	
NYHA class					
I		86 (3.9%)	64 (3.9%)	22 (3.7%)	0.756
II		695 (31.3%)	504 (30.8%)	191 (32.5%)	
III–IV		1442 (64.9%)	1067 (65.3%)	375 (63.8%)	
Rhythm	2232				
Sinus		1680 (75.3%)	1353 (82.7%)	327 (54.9%)	<0.001
AF		391 (17.5%)	266 (16.3%)	125 (21.0%)	
Atrial pacing		161 (7.2%)	17 (1.0%)	144 (24.2%)	
Conduction	2234				
Normal		175 (7.8%)	152 (9.3%)	23 (3.8%)	<0.001
RBBB		198 (8.9%)	145 (8.9%)	53 (8.8%)	
LBBB		1493 (66.8%)	1213 (74.2%)	280 (46.7%)	
Non-specific		193 (8.6%)	115 (7.0%)	78 (13.0%)	
Ventricular pacing		175 (7.8%)	9 (0.6%)	166 (26.7%)	
QRS (ms)	2226	158 (138–176)	154 (136–170)	174 (150–196)	<0.001
≤130 ms		420 (18.9%)	347 (21.2%)	73 (12.4%)	<0.001
130–150 ms		487 (21.9%)	405 (24.8%)	82 (13.9%)	
>150 ms		1319 (59.3%)	883 (54.0%)	436 (73.8%)	
ACEi/ARB/ARNI	2257	1945 (86.2%)	1442 (87.1%)	503 (83.7%)	0.040
BB	2257	1919 (85.0%)	1399 (84.5%)	520 (86.5%)	0.230
MRA	2256	1368 (60.6%)	1013 (61.2%)	355 (59.1%)	0.358
Loop diuretic	2244	1419 (63.2%)	1006 (61.1%)	413 (69.2%)	<0.001
Amiodarone	2252	514 (22.8%)	321 (19.4%)	193 (32.2%)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy with defibrillator; eGFR, estimated glomerular filtration rate; ICMP, ischaemic cardiomyopathy; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RBBB, right bundle branch block.

(26.6%), while the remaining were *de novo* implantation procedures. As illustrated in *Figure 1*, the proportion of upgrade procedures remained stable over time before 2017 (between 23.9% and 27.1%). Yet, a marked increase was noted in the last 3 years of the registry (2017 to 2019) with a proportion of 34.2%.

Patients who underwent CRT upgrade were less likely female, had a slightly poorer renal function, and more frequently suffered from ischaemic cardiomyopathy. They more often underwent upgrade to CRT using an epicardial lead. Approximately half of patients who received a CRT upgrade had a left bundle branch block (LBBB) just prior to the upgrade procedure, while this was three out of four patients for *de novo* CRT procedures. Further, patients who received a CRT upgrade were less often on renin–angiotensin–aldosterone system inhibitors, but more



	Before 2008	2008-2010	2011-2013	2014-2016	2017-2019
Upgrade from PM	21.4%	19.1%	12.9%	16.4%	25.3%
Upgrade from ICD	5.7%	7.0%	11.0%	8.5%	8.8%
Upgrade total	27.1%	26.1%	23.9%	24.9%	34.2%

Figure 1 Proportion of upgrade procedures over time. ICD, implantable cardioverter-defibrillator; PM, pacemaker.

frequently on amiodarone and loop diuretics. There was no difference in LVEF as absolute measurement, but patients who underwent an upgrade had more often an intermediate LVEF between 35% and 50%.

Among CRT upgrades, 410 patients (67.8%) were upgraded from a pacemaker while 195 patients (32.2%) received CRT upgrade from an ICD. A comparison between upgrades from pacemaker and ICD is shown in *Table 2*. Patients who were upgraded from an ICD were younger, more frequently had an ischaemic cardiomyopathy, and showed a lower baseline LVEF. Patients who were upgraded from a pacemaker had more frequently a paced rhythm in atrium and ventricle and were less often on guideline-directed optimal medical therapy.

Endpoint analysis

The mean overall follow-up was 3.6 ± 2.7 years. Endpoint analysis is summarized in *Table 3*.

Primary composite endpoint of all-cause mortality, heart transplantation or ventricular assist device implantation

During follow-up, the primary composite endpoint occurred in 656 patients (29.2%). A total of 590 patients (23.2%) died during the follow-up, 56 (4.0%) underwent heart transplantation, and 34 (2.5%) underwent ventricular assist device implantation. Kaplan–Meier graphs for endpoints are displayed in *Figure 2*. The incidence rate of the composite endpoint was 8.0%/year (95% confidence interval [CI] 7.4–8.6%) and was significantly higher in patients who underwent CRT upgrade procedures compared to *de novo* implantations (10.8%/year, 95% CI 9.5–12.4% vs. 7.1%/year, 95% CI 6.5–7.8%; *Figure 2A*, log-rank $p < 0.001$). There was no difference between upgrade from a pacemaker and from an ICD with regard to the composite endpoint (*Figure 2B*, $p = 0.188$). In univariable (hazard ratio [HR] 1.55, 95% CI 1.32–1.83) and multivariable Cox regression analysis (HR 1.27, 95% CI 1.06–1.51) device upgrades were associated with higher hazard rates to reach the composite endpoint (*Table 3* and online supplementary *Table S1A,B*). In the multivariable model, these higher hazard rates were present both for upgrades from pacemakers (HR 1.24, 95% CI 1.02–1.52) and from ICDs (HR 1.30, 95% CI 1.01–1.69) (online supplementary *Table S1B*). Besides upgrade to CRT, epicardial leads, ischaemic cardiomyopathy, diabetes mellitus, stroke, and estimated glomerular filtration rate (eGFR) as per chronic kidney disease stage were associated with higher hazard rates for the composite endpoint, while female sex, a higher baseline LVEF, and use of angiotensin blocking agents were associated with lower hazard rates (online supplementary *Table S1B*).

First heart failure admission

Heart failure admission data were present for 1329 patients from Leuven and Zürich. A total of 373 patients (28.1%) had at least one admission for heart failure after CRT implantation. The overall incidence for first heart failure admission was 7.8%/year (95% CI 7.0–8.6%) and was significantly higher in patients who underwent CRT upgrade procedures compared to *de novo* implantations (11.8%/year, 95% CI 9.9–14.1% vs. 6.6%/year, 95% CI 5.8–7.5%; log-rank $p < 0.001$; *Figure 2C*). There was no difference between upgrade from a pacemaker and upgrade from an ICD regarding first heart failure admissions ($p = 0.303$; *Figure 2D*). In univariable (HR 1.67, 95% CI 1.34–2.08) and multivariable Cox regression analysis (HR 1.55, 95% CI 1.24–1.94) device upgrades were associated with higher hazard rates for first heart failure admission (*Table 3* and online supplementary *Table S2A,B*). In the multivariable model, these higher hazard rates were present both for upgrades from pacemakers (HR 1.48, 95% CI 1.15–1.91) and from ICDs (HR 1.70, 95% CI 1.19–2.41) (online supplementary *Table S2B*). Besides upgrade to CRT, ischaemic cardiomyopathy, use of amiodarone, and eGFR as per chronic kidney disease stage were associated with higher hazard rates for first heart failure admission, while female sex was associated with lower hazard rates (online supplementary *Table S2B*).

Propensity score-matched analysis

After propensity score matching a total of 976 patients, 488 matched pairs, were available for analysis of the primary composite endpoint. The standardized mean differences of all included variables were reduced after matching and below the predetermined threshold (*Figure 3A*). In univariable and multivariable Cox regression analysis after propensity score matching upgrade procedures were associated with a higher chance to reach the composite endpoint (*Table 3* and online supplementary *Table S1C*). This was present for both upgrades from pacemakers (HR 1.33, 95% CI 1.03–1.70) and ICDs (HR 1.40, 95% CI 1.01–1.95).

After propensity score matching on all patients with data available on heart failure admission, 277 matched pairs, or 554 patients, were available for further analysis (*Figure 3B*). Further, upgrade procedures remained associated with an increased chance for a first heart failure admission (*Table 3* and online supplementary *Table S2C*). Again, this was present for both upgrades from pacemakers (HR 1.67, 95% CI 1.17–2 0.38) and ICDs (HR 1.94, 95% CI 1.21–3.10).

Table 2 Direct comparison of upgrade from pacemaker or from implantable cardioverter-defibrillator

Variable	Upgrade from PM	Upgrade from ICD	*p*-value
Patients, *n*	410 (67.8%)	195 (32.2%)	
Age at implant (years)	71.8 (62.8–77.9)	68.5 (60.1–74.7)	0.001
Female sex	87 (21.2%)	32 (16.4%)	0.164
CRT-D	215 (52.6%)	190 (97.4%)	<0.001
Epicardial LV lead	32 (7.9%)	23 (12.0%)	0.108
ICMP	187 (46.1%)	112 (57.4%)	0.009
Hypertension	268 (65.7%)	131 (67.2%)	0.717
Dyslipidaemia	257 (63.3%)	145 (74.7%)	0.005
Stroke	48 (11.8%)	25 (12.8%)	0.726
Diabetes mellitus	111 (27.1%)	40 (20.5%)	0.081
LVEF (%)	29.0 (22.0–35.0)	25.0 (20.0–30.0)	0.004
≤35%	321 (79.7%)	169 (89.9%)	0.008
35–50%	76 (18.9%)	18 (9.6%)	
>50%	6 (1.5%)	1 (0.5%)	
eGFR (ml/min/1.73 m^2)	51.1 (36.9–70.4)	48.0 (34.2–66.2)	0.101
CKD 1–2	165 (40.8%)	68 (36.6%)	0.490
CKD 3a	82 (20.3%)	36 (19.4%)	
CKD 3b	96 (23.8%)	45 (24.2%)	
CKD 4–5	61 (15.1%)	37 (19.9%)	
NYHA class			
I	21 (5.3%)	1 (0.5%)	0.005
II	119 (29.8%)	72 (38.3%)	
III–IV	260 (65.0%)	115 (61.2%)	
Rhythm			
Sinus	184 (45.1%)	143 (76.1%)	<0.001
AF	84 (20.6%)	41 (21.8%)	
Paced	140 (34.3%)	4 (2.1%)	
Conduction			
Normal	17 (4.2%)	6 (3.1%)	0.037
RBBB	30 (7.4%)	23 (11.9%)	
LBBB	179 (44.0%)	101 (52.3%)	
Non-specific	56 (13.8%)	22 (11.4%)	
Paced	125 (30.7%)	41 (21.2%)	
QRS (ms)	180 (154–200)	166 (144–186)	<0.001
≤130 ms	48 (11.9%)	25 (13.3%)	0.053
130–150 ms	47 (11.7%)	35 (18.6%)	
>150 ms	308 (76.4%)	128 (68.1%)	
ACEi/ARB/ARNI	333 (81.2%)	170 (89.0%)	0.016
BB	343 (83.7%)	177 (92.7%)	0.003
MRA	223 (54.4%)	132 (69.1%)	0.001
Loop diuretic	282 (69.5%)	131 (68.6%)	0.830
Amiodarone	97 (23.7%)	96 (50.3%)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy with defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; ICMP, ischaemic cardiomyopathy; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PM, pacemaker; RBBB, right bundle branch block.

Discussion

In this large, multicentre CRT registry patients who underwent a CRT upgrade procedure had a higher incidence of the primary composite endpoint, encompassing all-cause mortality, heart transplantation, or ventricular assist device implantation, when compared to *de novo* CRT implantations. Similarly, the incidence for a first heart failure admission after CRT was higher in patients who underwent a CRT upgrade procedure. These higher incidences were observed in both patients who were upgraded from pacemakers and those who were upgraded from ICDs.

Importantly, the participating centres of this CRT registry included all patients fulfilling the inclusion criteria resulting in a large, real-world population with unprecedented longitudinal

Table 3 Endpoint analysis for upgrade to cardiac resynchronization therapy

Endpoint	Prevalence			Regression before PSM						Regression after PSM					
				Univariable			Multivariable			Univariable			Multivariable		
	De novo	Upgrade	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Primary composite[a]	446 (27.0%)	210 (34.9%)	<0.001	1.55	1.32–1.83	<0.001	1.27	1.06–1.51	0.008	1.39	1.11–1.75	0.004	1.35	1.08–1.70	0.010
First HF admission[a]	247 (25.8%)	126 (33.8%)	0.004	1.67	1.34–2.08	<0.001	1.55	1.24–1.94	<0.001	1.45	1.09–1.93	0.011	1.74	1.26–2.41	0.001

The complete multivariable models are available in online supplementary *Tables S1* and *S2*.
CI, confidence interval; HF, heart failure; HR, hazard ratio; PSM, propensity score matching.
[a]Cox proportional hazard regression.

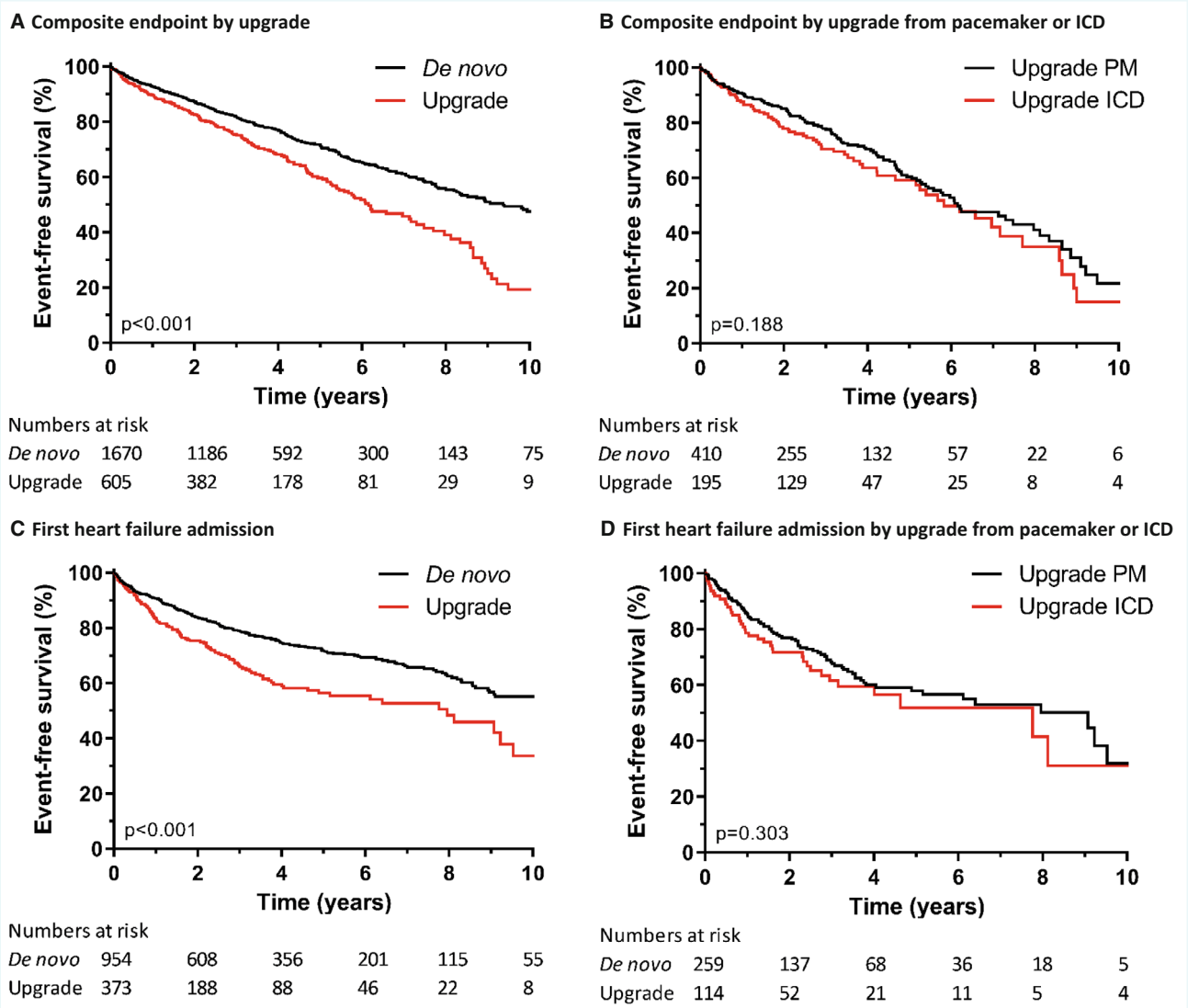


Figure 2 Kaplan–Meier survival analyses. (*A*) Composite endpoint by upgrade. (*B*) Composite endpoint by upgrade from pacemaker (PM) or implantable cardioverter-defibrillator (ICD). (*C*) First heart failure admission. (*D*) First heart failure admission by upgrade from PM or ICD.

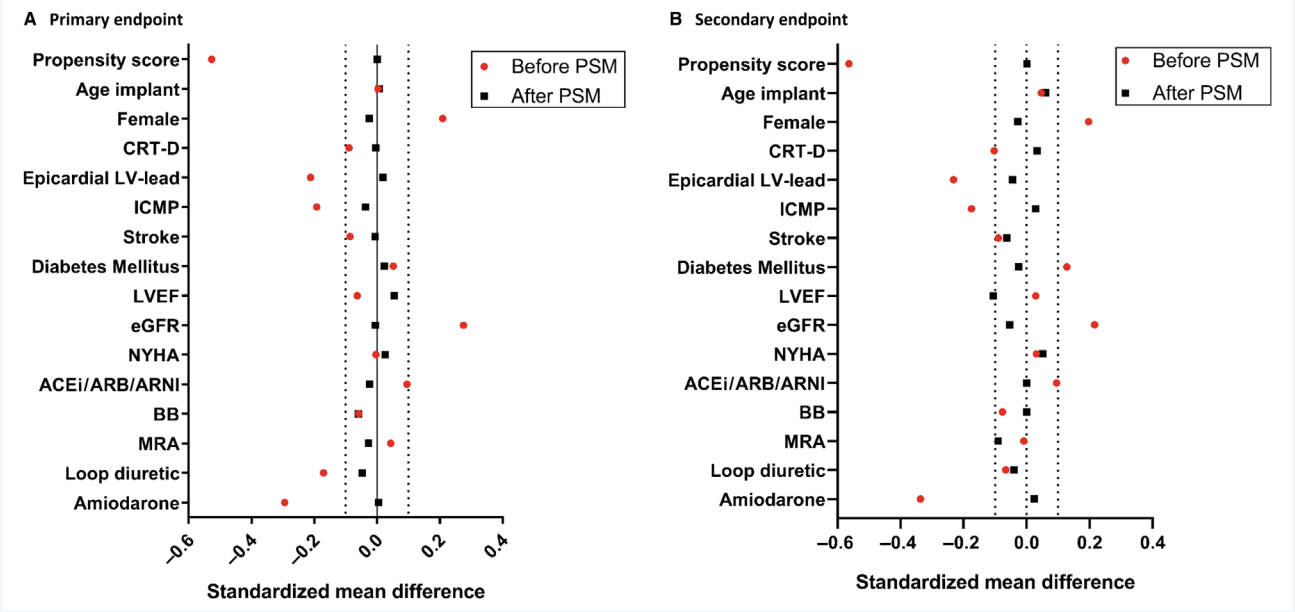


Figure 3 Mean standardized differences plot before and after propensity score matching (PSM). (*A*) Primary endpoint. (*B*) Secondary endpoint. Plot of standardized mean differences (Cohen's d) for the covariates included in the propensity score before and after matching. The dashed lines indicate the −0.1 and 0.1 threshold. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT-D, cardiac resynchronization therapy with defibrillator; eGFR, estimated glomerular filtration rate; ICMP, ischaemic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

follow-up, including both upgrades from pacemaker and from ICD as well as upgrades to CRT-P and CRT-D. As such, the inclusion period extends over almost 18 years during which patient selection, procedural methods, and device programming have evolved.[1,9,10] Patient characteristics were comparable with previously reported registries, including the higher proportion of patients with non-ischaemic cardiomyopathy and LBBB.[8,11–13] Patients who are referred for an upgrade to CRT are a very advanced-stage heart failure cohort with a high frequency of comorbidities.[14] Schwertner *et al.*[15] reported on a single-centre retrospective registry of similar size and follow-up. After propensity score matching, they no longer observed any difference in the primary composite endpoint.[15] In comparison to the study by Schwertner *et al.*, we performed a propensity score matched analysis with more variables in a smaller population, including variables such as stroke, diabetes mellitus, epicardial left ventricular leads and upgrade to CRT-D. All of these variables were independently associated with the primary composite endpoint in multivariable Cox regression analysis. Approximately half of our patients who underwent upgrade to CRT had a LBBB prior to the upgrade procedure, either due to presence of pre-existing LBBB prior to the implant of their first device or due to progression to LBBB during the period they had a pacemaker or ICD. Therefore, some of these patients may have fulfilled contemporary CRT indication criteria before their upgrade to CRT, however this could not be reliably ascertained retrospectively. The remaining difference in clinical outcome after propensity score matching most likely can be attributed to unknown or unavailable confounders, such as the difference in left ventricular remodelling prior to CRT procedure or the presence and extent of fibrosis. Identifying these unknown confounders in the future is important to improve the understanding of the differences in outcome.

An important note to this study is the lack of a true control population of patients who were eligible for a CRT upgrade procedure but did not receive the upgrade. However, in daily clinical practice, this true control population does not exist as comparable patients who are not upgraded to CRT most likely have a good clinical reason why a CRT upgrade was withheld. Therefore, the results of our analysis should not be interpreted as advising against CRT upgrade procedures. The observed higher incidence of the composite endpoint does not imply that there was no clinical benefit. A large recent meta-analysis by Kaza *et al.*,[16] including only patients with upgrade from pacemaker or ICD to CRT, showed significant improvement in LVEF, left ventricular end-systolic volume, New York Heart Association (NYHA) class, peak exercise oxygen capacity, and quality of life. A direct comparison between patients with *de novo* CRT and upgrade to CRT was, for example, provided by Foley *et al.*[5] who described similar clinical improvement in NYHA class, 6-min walking distance, and quality of life scores. Rather, the higher incidence of the composite endpoint, as observed in our study, may in part be related to patient characteristics, such as worse renal function and more unstable arrhythmias (more on amiodarone), in other words, a sicker patient population in general. Higher mortality rates in patients with upgrades have been

reported with both increased in-hospital and remote mortality.[8,17] The higher event rates in patients upgraded from ICDs compared to patients upgraded from pacemakers suggests a crucial role in the pre-existing underlying cardiomyopathy for the risk of all-cause mortality, independent of ischaemic or non-ischaemic aetiologies, such as the time since symptom onset.[18] While a large proportion of patients will respond in the first few months after CRT,[19] a lower improvement in LVEF in patients with upgrade from ICD and a higher proportion of late responders have been described.[8,20,21] Late responders are more frequently older patients with ischaemic cardiomyopathy.[20,21] On the other hand, patients who are upgraded from pacemaker therapy more likely reflect pacing-induced heart failure successfully reversed by resynchronization therapy. This is due to pacing-induced dyssynchrony and more remaining capacity to remodel than patients with underlying structural abnormalities. In a prospective registry, Christoph *et al.*[22] showed that in patients with newly diagnosed pacing-induced cardiomyopathy, CRT upgrade was associated with improvement in LVEF and functional capacity. Similar findings in patients upgraded from pacemaker therapy were recently reported in a meta-analysis which included 16 small studies (total $n = 924$).[23] Along this line, Gage *et al.*[24] found that patients with higher ventricular pacing proportions before upgrade to CRT had a larger increase in LVEF after 1 year of follow-up. Further, Stankovic *et al.*[25] described higher survival rates after CRT upgrade in patients with right ventricular pacing and mechanical dyssynchrony when compared to patients with right ventricular pacing without mechanical dyssynchrony. The recently published results of the BUDAPEST-CRT Upgrade study showed that in patients with pacemakers or ICDs with a reduced LVEF and a right ventricular pacing percentage ≥20%, upgrade to CRT-D was associated with a reduced risk of the composite endpoint (all-cause mortality, heart failure admission, or absence of reverse remodelling) when compared to ICD therapy.[26] In this study, the difference in outcome was largely driven by the absence of reverse remodelling and heart failure admissions. This study strongly re-iterates the importance of upgrading to CRT in eligible patients. The results of the BUDAPEST-CRT trial should be seen in line conjunction with our findings. In the assumption that the relative treatment effect of CRT in reducing heart failure events is almost the same in *de novo* implants versus upgrades, the absolute treatment effect in reducing heart failure events might be larger in upgrades as our observational data show that these patients have the highest event rate.

The question raises on how the outcome in patients eligible for upgrade to CRT can be further improved. As observed in *Figure 1*, this question remains relevant in the coming decades given the large contemporary population of patients with pre-existing pacemakers and ICDs. This requires reflecting on apical lead positioning in patients implanted with ICDs who might require addition of a left ventricular lead upon upgrade versus upfront conduction system pacing with a back-up shock lead. In fact, pacing-induced or pacing-triggered cardiomyopathy may present as a spectrum of clinical presentations and should be defined beyond changes in LVEF, including for example the increased incidence of atrial fibrillation and heart failure hospitalizations in patients with LVEF >50%.[27] The new era of conduction system pacing has to be backed up by randomized controlled trials in this area of research, particularly regarding long-term, hard clinical endpoints. Additionally, it needs to be recognized that patients for instance with an ICD that have progressive QRS widening often exhibit a phenotype of progressive myocardial remodelling despite optimal medical therapy. These patients might often have features of advanced heart failure. Therefore, physicians caring of these patients might need to evaluate the appropriate timing to initiate advanced heart failure evaluations for assist device or heart transplantation. In the meantime, registries should be explored to elucidate the association of ventricular pacing percentage, underlying cardiomyopathy, and CRT response on the timing and outcome of upgrade to CRT, acknowledging the inherent limitations, particularly compared to the gold standard of randomized controlled trials.

Limitations

First, the retrospective study design may have had a limited impact on endpoint ascertainment. Second, the number of available biochemical and echocardiographic variables was limited as only variables in common between the participating centres were included in the analysis. Third, relevant variables, such as left ventricular lead position, CRT programming, biventricular pacing percentage, and ventricular arrhythmia burden, could not be collected. Moreover, a selection bias for CRT implantation cannot be excluded, and collection of the clinical indication for upgrade to CRT or percentage ventricular pacing (differentiating chronic ventricular pacing and disease progression) could not be collected in detail in all centres. Fourth, despite propensity score matching residual bias by unmeasured confounders could still explain the relation between upgrades and worse clinical outcome. Fifth, peri- and post-procedural complications were not available for all patients. Since retrospective adjudication of procedural complications may be biased, we refrained from reporting the available complications. Finally, as with every registry, our data report associations without inferring causality of the observed effects.

Conclusions

Our data indicate that among patients implanted with a CRT, those who underwent an upgrade from pacemaker or ICD, have a higher likelihood of all-cause mortality and heart failure admissions when compared to those with *de novo* CRT implantations. Patients who are referred for a CRT upgrade are a very advanced-stage heart failure cohort with a high frequency of comorbidities. Importantly, these results do not imply that CRT upgrade procedures are not beneficial but describe a yet unknown and important difference between two patient populations. As approximately one in three CRT procedures is an upgrade to CRT procedure, this area of research needs to be explored in more detail in order to refine patient selection and define the best timing for CRT upgrades.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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