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Long-term clinical outcomes of cardiac resynchronization therapy with or without defibrillation: impact of the aetiology of cardiomyopathy

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Aims There is a continuing debate as to whether cardiac resynchronization therapy-defibrillation (CRT-D) is superior to CRT-pacing (CRT-P), particularly in patients with non-ischaemic cardiomyopathy (NICM). We sought to quantify the clinical outcomes after primary prevention of CRT-D and CRT-P and identify whether these differed according to the aetiology of cardiomyopathy.

Methods and results Analyses were undertaken in the total study population of patients treated with CRT-D ($n = 551$) or CRT-P ($n = 999$) and in propensity-matched samples. Device choice was governed by the clinical guidelines in the United Kingdom. In univariable analyses of the total study population, for a maximum follow-up of 16 years (median 4.7 years, interquartile range 2.4–7.1), CRT-D was associated with a lower total mortality [hazard ratio (HR) 0.72] and the composite endpoints of total mortality or heart failure (HF) hospitalization (HR 0.72) and total mortality or hospitalization for major adverse cardiac events (MACE; HR 0.71) (all $P < 0.001$). After propensity matching ($n = 796$), CRT-D was associated with a lower total mortality (HR 0.72) and the composite endpoints (all $P < 0.01$). When further stratified according to aetiology, CRT-D was associated with a lower total mortality (HR 0.62), total mortality or HF hospitalization (HR 0.63), and total mortality or hospitalization for MACE (HR 0.59) (all $P < 0.001$) in patients with ischaemic cardiomyopathy (ICM). There were no differences in outcomes between CRT-D and CRT-P in patients with NICM.

Conclusion In this study of real-world clinical practice, CRT-D was superior to CRT-P with respect to total mortality and composite endpoints, independent of known confounders. The benefit of CRT-D was evident in ICM but not in NICM.

Keywords Cardiac resynchronization therapy • Implantable cardioverter-defibrillator • Heart failure • Cardiomyopathy • Aetiology • Sudden cardiac death • Mortality • Outcome

Introduction

Cardiac resynchronization therapy (CRT) has revolutionized the treatment of patients with heart failure (HF), left ventricular (LV) systolic dysfunction, and a prolonged QRS duration. Besides prolonging survival, CRT also reduces HF hospitalization and improves symptoms, exercise capacity, and quality of life.[1]

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What's new?

- There is a debate as to whether cardiac resynchronization therapy-defibrillation (CRT-D) is superior to CRT-pacing (CRT-P), particularly in patients with non-ischaemic cardiomyopathy (NICM).
- In propensity-matched samples, we found that CRT-D was associated with a lower total mortality and the composite endpoints of total mortality or heart failure hospitalization and total mortality or hospitalization for major adverse cardiac events.
- When stratified according to aetiology, CRT-D was associated with a lower total mortality and composite endpoints in ischaemic cardiomyopathy, but not in NICM.

There is a continuing debate as to whether CRT-defibrillation (CRT-D) is superior to CRT-pacing (CRT-P). The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) study showed that CRT-D leads to a greater survival benefit than optimal pharmacological therapy but was underpowered to compare CRT-D with CRT-P. On the other hand, CRT-P has been shown to reduce sudden cardiac death (SCD),[2] an effect that is probably due to LV reverse remodelling. In this context, there is no firm evidence from metanalyses of randomized controlled trials of a survival benefit from CRT-D over CRT-P.[3] Whether or not these factors have influenced device choice, there has been a wide variation in the usage of CRT-P than CRT-D, ranging from 14% for CRT-P in the USA[4] to 30% in Japan and around 48% in the United Kingdom.[5] Following the recent publication of the DANISH (Defibrillator Implantation in Patients with Nonischaemic Systolic Heart Failure) study,[6] a European survey has shown that CRT-P is being used in preference to CRT-D in patients with non-ischaemic cardiomyopathy (NICM).[7]

This study of real-world clinical practice explores survival and other clinical outcomes of CRT-P and CRT-D over a period of 16 years. We also focus on the influence of ischaemic cardiomyopathy (ICM) and NICM on clinical outcomes.

Methods

Patients were recruited from two centres (Good Hope Hospital and Queen Elizabeth Hospital, Birmingham, UK) from October 2000 to January 2017. Implantation practice was governed by the UK's National Institute of Clinical Excellence (NICE) guidelines, which before 2007 recommended CRT-D only in the setting of secondary prevention. After 2007, NICE recommended CRT-P rather than CRT-D for patients with NICM.[8] With a subsequent NICE guideline change in 2014 recommending CRT-D in NICM,[8] the proportion of CRT-D recipients increased thereafter. This study was approved by the local ethics committee and/or the local Clinical Audit Departments and conforms with the Declaration of Helsinki.

Device therapy

Device implantation was undertaken using standard transvenous techniques under local anaesthesia and intravenous sedation. After implantation, patients were followed up in dedicated device therapy clinics. Before 2013, patients in sinus rhythm underwent echocardiographic optimization using an iterative technique prior to discharge and at every scheduled visit thereafter. Routine echocardiographic optimization was abandoned in 2013 when targeted optimization was undertaken in symptomatic non-responders. Backup atrial pacing was set at 60 b.p.m., and the pacing mode was set to DDDR with an inter-ventricular delay of 0–20 ms (LV first), according to the implanter preference. In patients in permanent atrial fibrillation, right ventricular and LV leads were deployed, and a CRT generator or a dual-chamber generator was implanted. Programming to a ventricular triggered mode and atrioventricular junction ablation was undertaken according to physicians' discretion.

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 (MACE), which included hospitalization for HF, myocardial infarction, acute coronary syndrome, and arrhythmia [ventricular tachycardia (VT), ventricular fibrillation (VF) and atrial fibrillation]. Device-treated arrhythmias (appropriately treated with shocks or anti-tachycardia pacing) not leading to an unplanned hospitalization were not regarded as a hospitalization for MACE. Similarly, stroke and pulmonary embolism were not regarded as MACE. Ancillary endpoints included cardiac mortality, death from pump failure, and the composite endpoint of SCD or hospitalization for VT or VF. In composite endpoints, the first event was included in statistical analyses. Mortality data were collected through medical records and, where appropriate, from interviews with patients' caregivers. Data were collected retrospectively from medical records and interviews with care givers and entered into an electronic database. Clinical outcome data were collected every 6 months by investigators who were blinded to clinical and imaging data. Events were adjudicated by blinded investigators on a 6-monthly basis.

Cause and mode of death

A natural, unexpected death due to cardiac causes, heralded by an abrupt loss of consciousness within 1 h of the onset of acute symptoms was regarded as an SCD. Death from pump failure was defined as 'death after a period of clinical deterioration in signs and symptoms of HF despite medical treatment'.[9] Non-cardiac deaths and causes thereof were adjudicated on the basis of hospital records or correspondence from primary care physicians. Deaths were classified as 'unknown' if no definitive data were found in hospital or primary care records or from interviews with caregivers.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Normality was tested using the Shapiro–Wilk test. Comparisons between normally distributed continuous variables were made using analysis of variance with Scheffe's *F*-test for multiple comparisons. Categorical variables were analysed using χ^2 tests and Scheffe's *post hoc* test. The 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. Statistical analyses were undertaken using Stata14 (StataCorp, College Station, TX, USA). A two-sided P-value $\leq$0.05 was considered statistically significant.

Propensity matching

Variables selected for propensity matching between the CRT-D and the CRT-P groups included those which differed significantly at baseline and which emerged as predictors of the primary endpoint. Patients with similar propensity scores were selected using 1:1 nearest-neighbour matching within a specified caliper width (0.01). Each pair was used once and

unpaired cases were excluded from further analysis. The standardized difference was used to access balance in means or proportions between CRT-D and CRT-P recipients, and a difference of <10% was accepted for matched cohorts.

Results

Baseline characteristics

Over the study period, 1500 patients underwent primary prevention CRT-D [*n* = 551 (36.7%)] or CRT-P [*n* = 999 (66.6%)]. Of these, 252 patients with NICM were included in a previous study.[10] As shown in *Table 1*, CRT-D recipients were 3 years younger, were more often male, and were having ICM ($P < 0.001$). In addition, the CRT-D group had a greater proportion of patients with diabetes ($P = 0.016$) and hypertension ($P = 0.048$) but a lower proportion with atrial fibrillation ($P < 0.001$). Excluding patients with conventional indications for pacing and those who were upgraded from a pacemaker to CRT (*n* = 426), QRS duration was 4.3 ms shorter in CRT-D patients ($P < 0.001$). In addition, LBBB was less prevalent in CRT-D recipients ($P = 0.013$). A total of 314 (20.3%) patients had conventional indications for pacing (CRT-D: 15.1%, CRT-P: 23.1%; $P = 0.388$).

Table 1 Baseline characteristics

	CRT-D	CRT-P	*P*-value[a]
n	551	999	
Gender (male)	439 (79.67)	707 (70.77)	<0.001
Age (years)	70.1 ± 9	73.1 ± 11	<0.001
NYHA class	2.8 ± 0.6	3.1 ± 0.6	<0.001
I	34 (6.36)	15 (1.54)	<0.001
II	68 (12.71)	70 (7.17)	
III	401 (74.95)	699 (71.62)	
IV	32 (5.98)	192 (19.67)	
Aetiology (ischaemic)	415 (75.32)	437 (43.74)	<0.001
Co-morbidity			
Diabetes mellitus	140 (25.41)	201 (20.12)	0.016
Hypertension	141 (25.59)	303 (30.33)	0.048
CABG	144 (26.13)	143 (14.31)	<0.001
ECG variables			
Sinus rhythm	397 (72.05)	637 (63.76)	0.001
Atrial fibrillation[b]	154 (27.95)	362 (36.24)	
QRS morphology (LBBB)[c]	421 (78.69)	824 (83.83)	0.013
QRS duration (ms)[c]	150.8 ± 21	155.1 ± 21	0.001
Upgrades from pacemaker to CRT	67 (13.27)	193 (19.75)	0.002
Medications			
Loop diuretics	526 (98.32)	920 (95.14)	0.002
ACEIs/ARAs	500 (92.94)	850 (87.36)	0.001
Beta-blockers	416 (77.32)	591 (60.74)	<0.001
MRA	274 (50.93)	381 (39.16)	<0.001
LVEF	23.5 ± 9	24.8 ± 10	0.018

Variables are expressed as mean ± SD or *n* (%).
ACEI, angiotensin-converting enzyme inhibitors; ANOVA, analysis of variance; ARA, angiotensin receptor antagonists; CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; MRA, mineralocorticoid receptor antagonists.
[a]Refers to differences between the groups from ANOVA with Scheffe's *post hoc* test for continuous variables and from the χ^2 tests for categorical variables.
[b]Includes permanent, persistent and paroxysmal atrial fibrillation.
[c]Excludes patients who were upgraded from a pacemaker to CRT and patients with conventional indications for pacing.

Total study population

Total mortality was 205 of 551 (37.2%; 9.8 per 100 person-years) after CRT-D and 580 of 999 (58.1%; 13.5 per 100 person-years) after CRT-P. Cardiac mortality was 113 of 551 (20.5%; 4.4 per 100 person-years) after CRT-D and 384 of 999 (38.4%; 7.1 per 100 person-years) after CRT-P. Over a maximum follow-up period of 16 years [median 4.7 years, interquartile range (IQR) 2.4–7.1 for total surviving patients; median 4.1 years, IQR 2.2–6.7 for CRT-D; and median 5.1 years, IQR 2.8–8.1 for CRT-P], CRT-D was associated with a lower total mortality in the Kaplan–Meier survival analyses (log-rank $P < 0.001$) (*Figure 1*). In univariable Cox proportional hazards analyses, CRT-D was associated with a lower total mortality [HR 0.72, 95% confidence interval (CI) 0.61–0.84; *Table 2*].

Total mortality or HF hospitalization was 231 of 551 (41.9%; 11.9 per 100 person-years) after CRT-D and 627 of 999 (62.8%; 16.2 per 100 person-years) after CRT-P. In the Kaplan–Meier survival analyses, CRT-D was associated with a lower total mortality or HF hospitalization (log-rank $P < 0.001$; *Figure 1*). In univariable Cox proportional hazards analyses, CRT-D was associated with a lower total mortality or HF hospitalization (HR 0.72, 95% CI 0.62–0.84; *Table 2*).

Total mortality or hospitalization for MACE was 241 of 551 (43.7%; 12.8 per 100 person-years) after CRT-D and 652 of 999 (65.3%; 17.8 per 100 person-years) after CRT-P. In the Kaplan–Meier survival analyses, CRT-D was associated with a lower total mortality or hospitalization for MACE (log-rank $P = 0.005$; *Figure 1*). In univariable Cox proportional hazards analyses, CRT-D was associated with a lower total mortality or hospitalization for MACE (HR 0.71, 95% CI 0.61–0.82; *Table 2*).

Cause and mode of death

Over the follow-up period, 785 patients died. The cause of death was unknown in 142 patients [CRT-D: 58/551 (10.5%), CRT-P: 84/999 (8.4%); $P = 0.167$]. Of the 643 deaths of known cause, 497 (77.3%) were due to cardiac causes and 146 (22.7%) to non-cardiac causes. In CRT-P patients, 60 of 999 (6.0%) suffered an SCD and 315 of 551 (57.1%) died from pump failure. In CRT-D patients, 14 of 551 (2.54%) suffered an SCD and 96 of 551 (17.4%) died from pump failure (*Figure 2*).

Propensity-matched population

In univariable Cox proportional hazards analyses (*Table 2*), age, male gender, New York Heart Association (NYHA) class (III and IV), ischaemic aetiology, diabetes, atrial fibrillation, and no uptake of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor antagonists (ARAs) or beta-blockers emerged as significant predictors of total mortality. These variables, which differed significantly between the CRT-D and the CRT-P groups (*Table 1*), were included in propensity matching.

The propensity-matched sample, which included 796 patients, was well balanced for confounding variables (*Table 3*). As shown in *Figure 3*, CRT-D was associated with a lower total mortality (HR

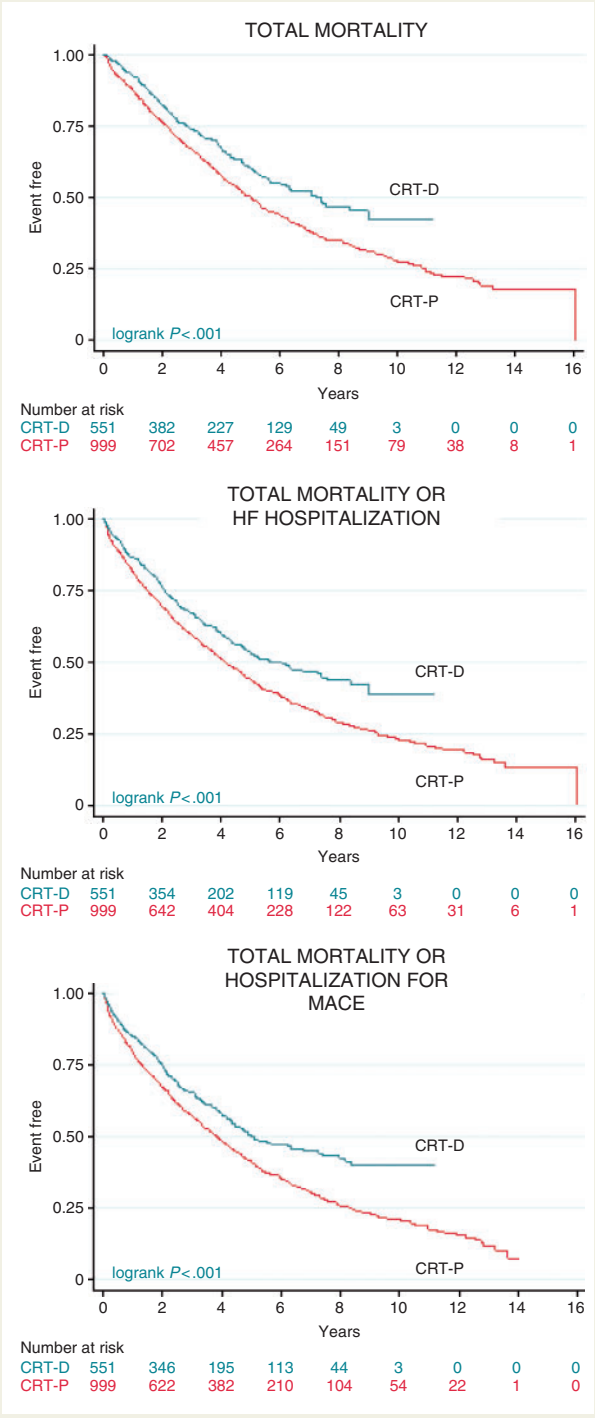

Figure 1 Primary and secondary endpoints according to the device type. The Kaplan–Meier survival curves for clinical outcomes according to the device type in the total patient population. CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; HF, heart failure; MACE, major adverse cardiovascular events.

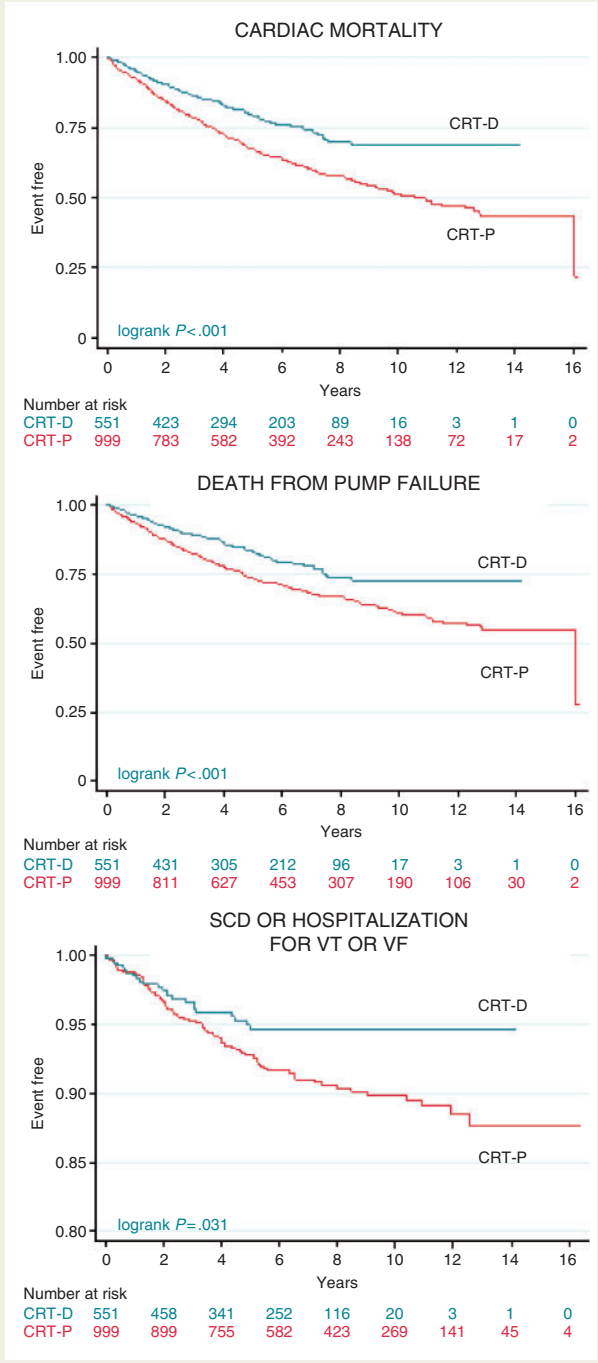

Figure 2 Ancillary endpoints according to the device type. The Kaplan–Meier survival curves for clinical outcomes according to the device type in the total patient population. CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; HF, heart failure; MACE, major adverse cardiovascular events; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

0.72, 95% CI 0.59–0.89), total mortality of HF hospitalization (HR 0.74, 95% CI 0.60–0.90), and total mortality or hospitalization for MACE (HR 0.70, 95% CI 0.58–0.85). In addition, CRT-D was associated with a lower cardiac mortality (HR 0.59, 95% CI 0.46–0.77), mortality from pump failure (HR 0.65; 95% CI 0.48–0.86), SCD (HR 0.49; 95% CI 0.25–0.98), and the combined endpoint of SCD or hospitalization for VT or VF (HR 0.51; 95% CI 0.30–0.88). When stratified according to the aetiology of cardiomyopathy, CRT-D was

Table 2 Univariable analyses[a]

	Total mortality				Total mortality or HF hospitalization				Total mortality or hospitalization for MACE			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Device type (CRT-D)	0.72	0.61	0.84	<0.001	0.72	0.62	0.84	<0.001	0.71	0.61	0.82	<0.001
Gender (male), *n* (%)	1.55	1.30	1.84	<0.001	1.38	1.18	1.63	<0.001	1.33	1.14	1.55	<0.001
Age (years)	1.03	1.02	1.04	<0.001	1.03	1.02	1.04	<0.001	1.02	1.02	1.03	<0.001
NYHA class												
III	1.77	1.21	2.60	0.003	1.49	1.08	2.05	0.016	1.62	1.18	2.22	0.003
IV	3.51	2.36	5.24	<0.001	3.14	2.23	4.43	<0.001	3.22	2.30	4.51	<0.001
Aetiology (ischaemic)	1.28	1.11	1.47	0.001	1.29	1.13	1.48	<0.001	1.36	1.19	1.56	<0.001
Co-morbidity												
Diabetes mellitus	1.15	0.97	1.36	0.100	1.20	1.03	1.41	0.023	1.21	1.03	1.41	0.018
Hypertension	0.96	0.82	1.12	0.571	1.01	0.87	1.17	0.948	0.99	0.86	1.15	0.937
ECG variables												
Atrial fibrillation[b]	1.29	1.11	1.49	0.001	1.21	1.05	1.39	0.008	1.18	1.03	1.35	0.021
QRS morphology (LBBB)[c]	0.97	0.81	1.16	0.711	0.89	0.75	1.05	0.155	0.88	0.74	1.03	0.116
QRS duration (ms)[c]	1.00	1.00	1.00	0.733	1.00	0.99	1.00	0.299	1.00	0.99	1.00	0.280
Upgrade from pacemaker to CRT	1.00	0.83	1.21	0.996	1.00	0.83	1.19	0.969	0.92	0.77	1.10	0.374
Medication												
Loop diuretics	1.27	0.90	1.81	0.178	1.47	1.03	2.09	0.032	1.25	0.90	1.74	0.187
ACEIs/ARAs	0.74	0.60	0.91	0.005	0.74	0.60	0.91	0.005	0.69	0.56	0.84	<0.001
Beta-blockers	0.69	0.60	0.80	<0.001	0.72	0.62	0.83	<0.001	0.72	0.63	0.83	<0.001
MRA	1.03	0.89	1.19	0.722	1.01	0.88	1.16	0.842	1.04	0.91	1.19	0.539
LVEF	0.99	0.99	1.00	0.100	1.00	0.99	1.00	0.360	1.00	0.99	1.00	0.271

ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin receptor antagonists; CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillation; HR, hazard ratio; MRA, mineralocorticoid receptor anatagonists.
[a]Results are expressed in terms of HRs and 95% CI from univariable Cox proportional hazards analyses.
[b]Includes permanent, persistent and paroxysmal atrial fibrillation.
[c]Excludes patients who were upgraded from a pacemaker to CRT and patients with conventional indications for pacing.

associated with a lower risk of total mortality (HR 0.62, 95% CI 0.49–0.79), total mortality or HF hospitalization (HR 0.63, 95% CI 0.50–0.79) and total mortality or hospitalization for MACE (HR 0.59, 95% CI 0.48–0.74). No difference in outcomes between CRT-D and CRT-P emerged in patients with NICM.

Aetiology

Crude total mortality, according to device type and HF aetiology, is shown in *Figure 4*. In univariable Cox proportional hazards analyses (*Table 2*), ischaemic aetiology was associated with higher total mortality (HR 1.28, 95% CI 1.11–1.47), total mortality or HF hospitalization (HR 1.29, 95% CI 1.13–1.48), and total mortality or hospitalization for MACE (HR 1.36, 95% CI 1.19–1.56). In the total study population, CRT-D was superior to CRT-P with respect to all clinical outcomes in ICM but not in NICM (data not shown). Similar findings emerged from the analyses of propensity-matched samples (*Figure 3*, *Table 4*).

Discussion

This study is unique insofar as it provides the longest clinical outcome follow-up of CRT-D and CRT-P recipients among randomized

Table 3 Characteristics of the propensity-matched sample

	CRT-D	CRT-P	*P*-value[a]
n	398	398	
Gender (male)	309 (77.64)	299 (75.13)	0.404
Age (years)	71.1 ± 9	71.0 ± 11	0.868
NYHA class	2.9 ± 0.5	2.9 ± 0.6	0.846
Aetiology (ischaemic)	282 (70.85)	284 (71.36)	0.876
Diabetes mellitus	92 (23.12)	99 (24.87)	0.561
Atrial fibrillation[b]	118 (29.65)	117 (29.40)	0.938
Medication			
ACEIs/ARAs	366 (91.96)	367 (92.21)	0.896
Beta-blockers	289 (72.61)	284 (71.36)	0.693

Variables are expressed as mean ± SD or *n* (%).
ACEI, angiotensin converting enzyme inhibitors; ANOVA, analysis of variance; ARA, angiotensin receptor antagonists; CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing.
[a]Refers to differences between the groups from ANOVA with Scheffe's *post hoc* test for continuous variables and from the χ^2 tests for categorical variables.
[b]Includes permanent, persistent and paroxysmal atrial fibrillation.

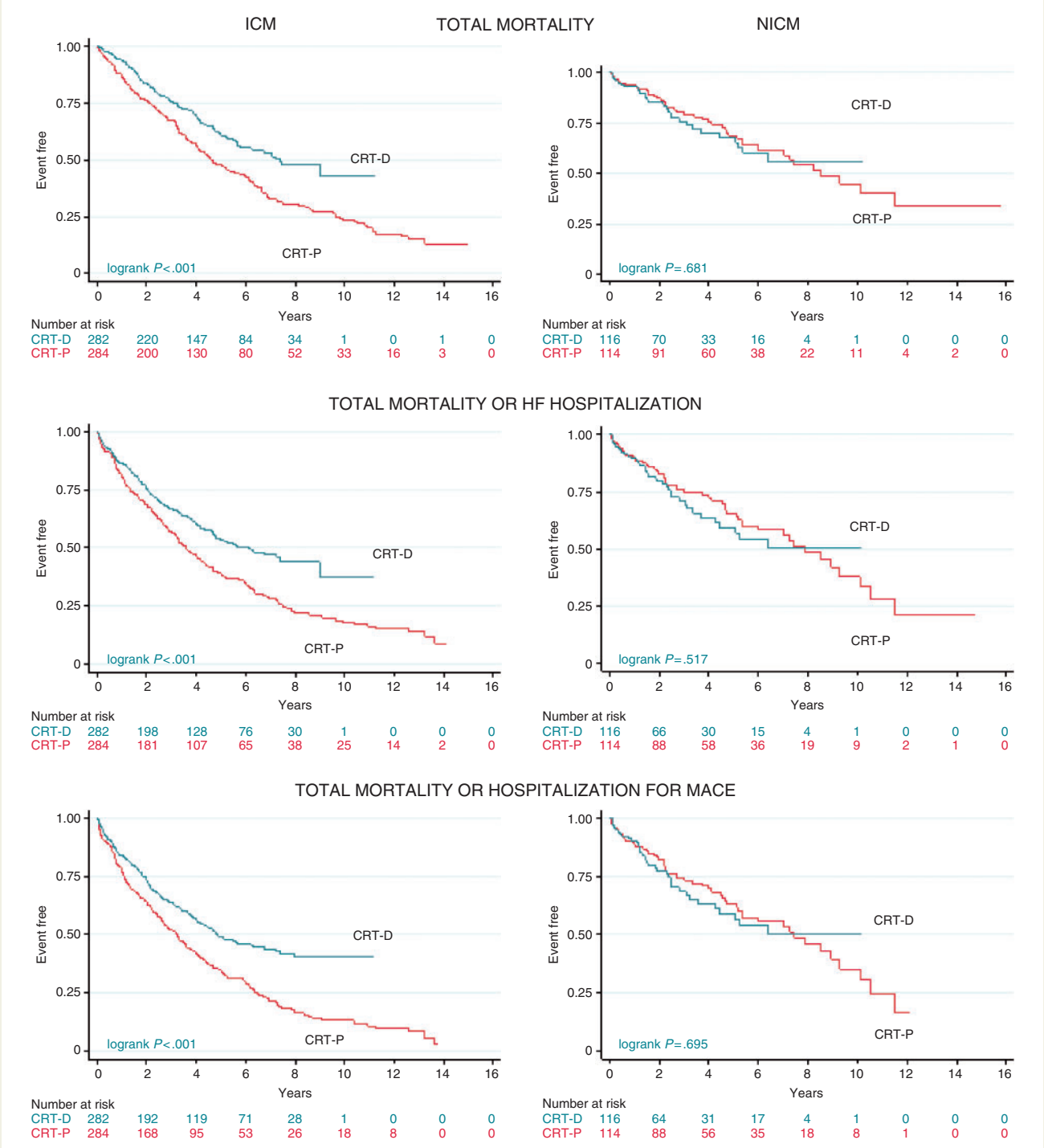

Figure 3 Primary and secondary endpoints according to the aetiology of cardiomyopathy in propensity-matched samples. The Kaplan–Meier survival curves for primary endpoints according to the device type and aetiology of cardiomyopathy. CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; HF, heart failure; ICM, ischaemic cardiomyopathy; MACE, major adverse cardiovascular events; NICM, non-ischaemic cardiomyopathy.

Table 4 Events and Cox proportional hazards analyses in the propensity-matched population[a]

	All (796)	CRT-D ($n = 398$)	CRT-P ($n = 398$)	HR	95% CI		*P*-value
All patients ($n = 796$)							
Total mortality	373	144	229	0.72	0.59	0.89	0.003
Total mortality or HF hospitalization	418	167	251	0.74	0.60	0.90	0.002
Total mortality or hospitalization for MACE	443	177	266	0.70	0.58	0.85	<0.001
Cardiac mortality	257	89	168	0.59	0.46	0.77	<0.001
Death from pump failure	207	73	134	0.65	0.48	0.86	0.003
SCD or hospitalization for VT/VF	63	19	44	0.51	0.30	0.88	0.015
ICM ($n = 566$)							
Total mortality	300	114	186	0.62	0.49	0.79	<0.001
Total mortality or HF hospitalization	333	131	202	0.63	0.50	0.79	<0.001
Total mortality or hospitalization for MACE	354	140	214	0.59	0.48	0.74	<0.001
Cardiac mortality	207	73	134	0.56	0.42	0.75	<0.001
Death from pump failure	168	60	108	0.60	0.44	0.83	0.002
SCD or hospitalization for VT/VF	53	17	36	0.54	0.30	0.97	0.039
NICM ($n = 230$)							
Total mortality	73	30	43	1.11	0.68	1.79	0.681
Total mortality or HF hospitalization	85	36	49	1.16	0.74	1.81	0.518
Total mortality or hospitalization for MACE	89	37	52	1.09	0.71	1.68	0.695
Cardiac mortality	50	16	34	0.68	0.37	1.25	0.213
Death from pump failure	39	13	26	0.77	0.39	1.54	0.464
SCD or hospitalization for VT/VF	10	2	8	0.32	0.07	1.51	0.151

ANOVA, analysis of variance; CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; HR, hazard ratio; ICM, ischaemic cardiomyopathy; MACE, major adverse cardiovascular events; MRA, mineralocorticoid receptor antagonists; NICM, non-ischaemic cardiomyopathy; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]Results are expressed in terms of HRs and 95% CIs from univariable Cox proportional hazards analyses of the propensity-matched sample for the comparison between CRT-D and CRT-P.

controlled trials or any other observational study. Several findings have emerged from the analyses of the total patient population and propensity-matched samples. First, after propensity matching, total mortality was 38% lower after CRT-D than after CRT-P. Second, total mortality or HF hospitalization and total mortality or hospitalization for MACE was also lower after CRT-D. Third, the superiority of CRT-D over CRT-P was observed in ICM but not in NICM. Fourth, predictors of survival after CRT-D compared with CRT-P included a younger age, female gender, NICM, a 'low' NYHA class (I and II), sinus rhythm, and a non-diabetic status and treatment with ACEIs/ARAs and/or beta-blockers.

Cardiac resynchronization therapy-defibrillation vs. cardiac resynchronization therapy-pacing in the total study population

Notwithstanding the limitations of comparing studies of different design and patient characteristics, our observed total mortality rate of 9.8% for CRT-D is within the range of that found in COMPANION study (12%)[11] and the European CRT Survey (8.6%).[12] For CRT-P, we have found a total mortality rate of 13.5%, which is also comparable to the 15% found in COMPANION study.[11]

In COMPANION study,[11] the only randomized controlled trial to include CRT-D and CRT-P recipients, no difference emerged in all-cause mortality between CRT-D (18%) and CRT-P (21%) after a median follow-up of 16 months. In the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial of CRT of patients with mild heart failure, CRT-D was associated with a lower mortality (HR = 0.35, $P = 0.003$) than CRT-P.[13] In a recent European registry of 1705 consecutive patients, CRT-D was superior to CRT-P over a follow-up of 2 years.[14] We too have found that CRT-D was superior to CRT-P. In the propensity-matched population, CRT-D was associated with a 28% lower total mortality. Moreover, CRT-D was associated in lower total mortality or HF hospitalization, total mortality or hospitalization for MACE, cardiac mortality, death from pump failure, and SCD or hospitalization for VT/VF.

Long-term follow-up

Some studies suggest that the benefit of CRT-D may be time limited and that CRT-D merely 'converts' a potential SCD into a death from other causes. In COMPANION study,[11] survival curves for CRT-D and CRT-P merged after 9 months. In a subanalysis of COMPANION study,[15] comparing CRT-D with CRT-P, CRT-D was associated with a reduction in SCD but not total mortality. Looi *et al.*[16] also observed a trend in favour of CRT-D at 1 year (HR 0.54, 95% CI 0.27–1.07, $P = 0.08$), but this was absent after 2.4 years. In contrast, we have found that over a much longer follow-up period (maximum 16 years;

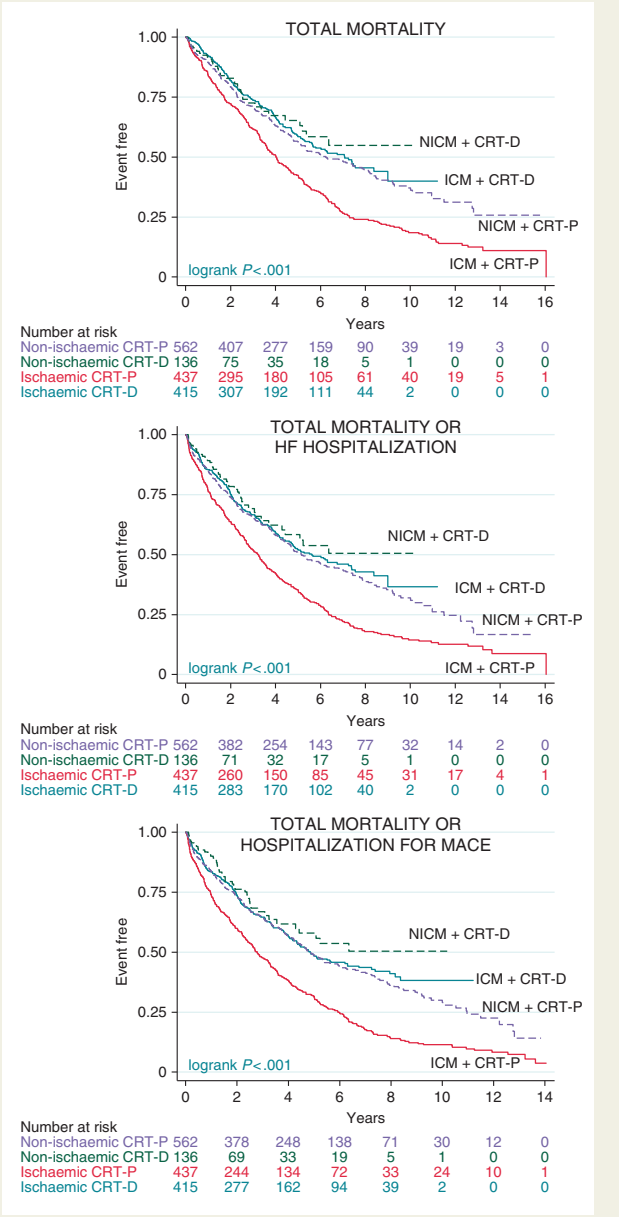

Figure 4 Survival curves according to the device type and the aetiology of cardiomyopathy. The Kaplan–Meier survival curves for clinical outcomes according to the device type and aetiology. CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; HF, heart failure; ICM, ischaemic cardiomyopathy; MACE, major adverse cardiovascular events; NICM, non-ischaemic cardiomyopathy.

median 4.7 years), survival curves for CRT-D and CRT-P continued to diverge. This suggests that the benefit of defibrillation persists in the long term.

Aetiology

A network meta-analysis of 13 randomized trials (12 638 patients) showed that CRT-D reduced total mortality by 19% compared with CRT-P, but it did not explore the effects of HF aetiology.[17] Our finding of better outcomes after CRT-D vs. CRT-P in ICM but not in NICM is consistent with several studies. Kutyifa *et al.*[18] showed no mortality benefit from CRT-D vs. CRT-P in a total cohort of 1122 patients, but when stratified according to aetiology, CRT-D was associated with a significant 30% reduction in all-cause mortality compared with CRT-P. In a recent multicentre, European cohort study of 5307 patients with DCM or ICM and no history of sustained ventricular arrhythmias, followed up over a mean of 3.45 years, Barra *et al.*[19] found that CRT-D was superior to CRT-P after propensity matching in ICM but not in NICM. The excess mortality in CRT-P patients was related to SCD in 8.0% of patients with ICM but in only 0.4% of those with NICM.

In our analyses, we included 698 patients with NICM, 25 of whom suffered an SCD. We should consider that higher numbers may be needed to show a benefit from CRT-D over CRT-P in NICM. In the National Institute Health and Care Excellence network meta-analysis undertaken prior to DANISH study, 1457 patients were needed to show a significant effect of ICDs on total mortality in NICM.[3] Even higher numbers were used in recent meta-analyses that include DANISH.[20] It is possible, therefore, that our analyses were underpowered to show a mortality benefit from CRT-D over CRT-P in patients with NICM.

We found that CRT-D was associated with a lower risk of death from pump failure in the total propensity-matched population (HR 0.65, $P = 0.003$). The reason as to why defibrillation should influence death from pump failure is unclear. We should consider, however, that some patients coded as having died from pump failure may have had ventricular arrhythmia treated with either anti-tachycardia therapy or defibrillation. Access to telemonitoring and device interrogation after death, neither of which was undertaken in this study, could have shed light on this issue.

Limitations

This study has all the limitations of an observational study. First, the lack of randomization does not discount the possibility that unobserved variables may have contributed to outcomes. Second, although we have attempted to correct for potential confounders, we have not quantified other co-morbidities nor frailty, a factor that often influences the choice of CRT-P over CRT-D. Third, we have not collected device data at the time of death. In this regard, we should consider that not all SCDs are necessarily arrhythmic and that some may be due to non-cardiac causes. Nevertheless, CRT-D may have prevented at least some of the 60 SCDs that occurred in CRT-P recipients. Finally, as this is an observational study, any parallels or discrepancies with randomized controlled trials should be interpreted with caution.

Conclusions

In this study of real-world clinical practice, we have shown that CRT-D is superior to CRT-P with respect to total mortality and composite endpoints, independent of known confounders. The benefit of CRT-D in terms of total mortality and the composite endpoints, however, was observed in ICM but not in NICM. Further studies are needed to identify subpopulations of patients with NICM with indications for CRT who may benefit from CRT-D.

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