ESC European Society of Cardiology

Europace (2023) **25**, 1–11
https://doi.org/10.1093/europace/euad141

CLINICAL RESEARCH

Improved prognosis after cardiac resynchronization therapy over a decade

Francisco Leyva [1]*, Abbasin Zegard [1,2], Peysh Patel[2], Berthold Stegemann [1,2], Howard Marshall [2], Peter Ludman [2], Joseph de Bono [2], Giuseppe Boriani [3], and Tian Qiu[2]

[1]Aston Medical Reseach Insitute, Aston Medical School, Aston University, Aston Triangle, Birmingham B4 7ET, UK; [2]Univeristy Hospitals Birmingham Queen Elizabeth, Mindelsohn Way, Birmingham B15 2WB, UK; and [3]Cardiology Division, Department of Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Via Universita 4, Modena 41100, Italy

Received 29 March 2023; accepted after revision 16 May 2023

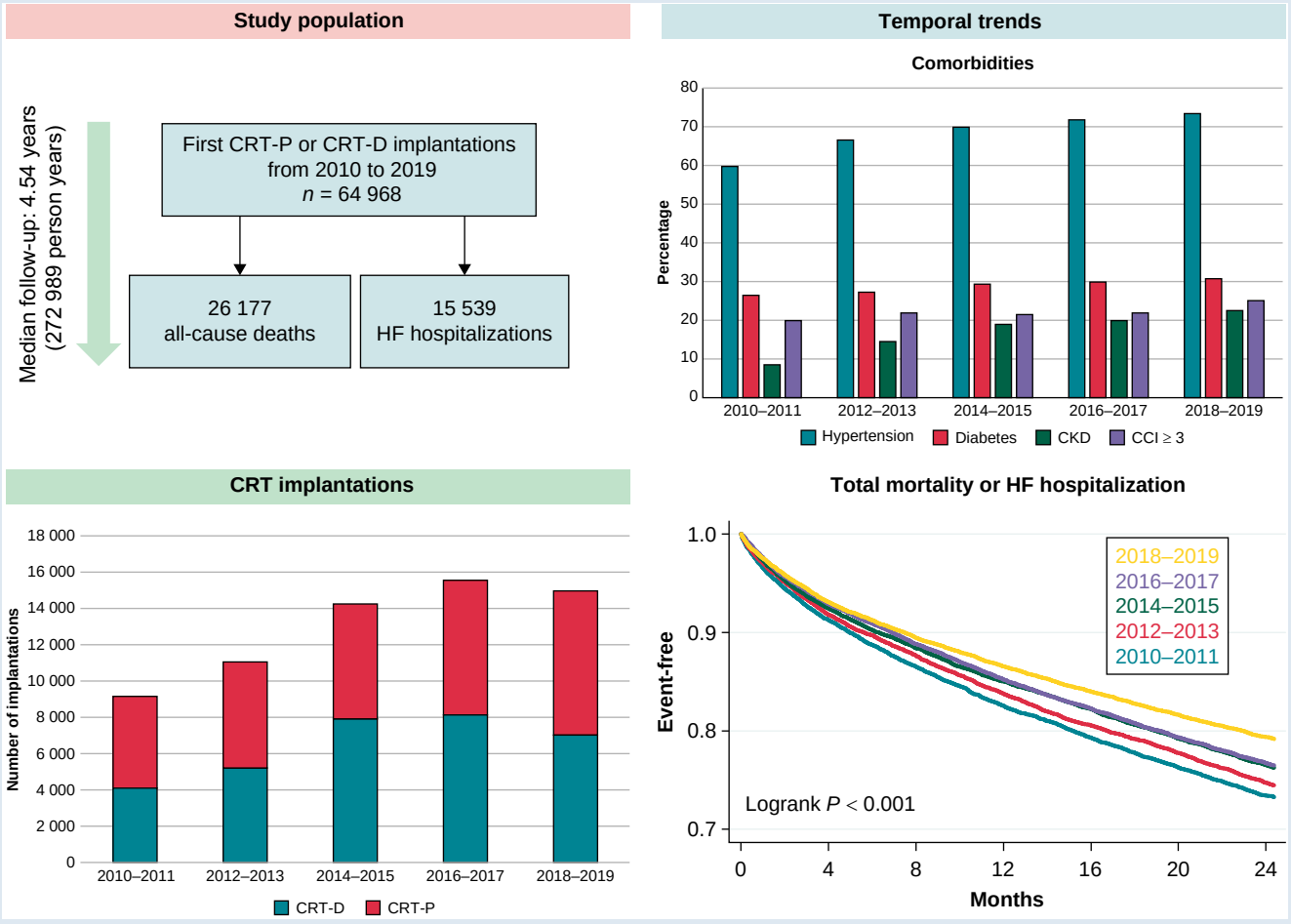
Aims The past decade has seen an increased delivery of cardiac resynchronization therapy (CRT) for patients with heart failure (HF). We explored whether clinical outcomes after CRT have changed from the perspective of an entire public healthcare system.

Methods and results A national database covering the population of England (56.3 million in 2019) was used to explore clinical outcomes after CRT from 2010 to 2019. A total of 64 698 consecutive patients (age 71.4 ± 11.7 years; 74.8% male) underwent CRT-defibrillation [$n = 32\,313$ (49.7%)] or CRT-pacing [$n = 32\,655$ (50.3%)] implantation. From 2010–2011 to 2018–2019, there was a 76% increase in CRT implantations. During the same period, the proportion of patients with hypertension (59.6–73.4%), diabetes (26.5–30.8%), and chronic kidney disease (8.62–22.5%) increased, as did the Charlson comorbidity index (CCI ≥ 3 from 20.0% to 25.1%) (all $P < 0.001$). Total mortality decreased at 30 days (1.43–1.09%) and 1 year (9.51–8.13%) after implantation (both $P < 0.001$). At 2 years, total mortality [hazard ratio (HR): 0.72; 95% confidence interval (CI) 0.69–0.76] and total mortality or HF hospitalization (HR: 0.59; 95% CI 0.57–0.62) decreased from 2010–2011 to 2018–2019, after correction for age, race, sex, device type (CRT-defibrillation or pacing), comorbidities (hypertension, diabetes, chronic kidney disease, and myocardial infarction), or the CCI (HR: 0.81; 95% CI 0.77–0.85).

Conclusions From the perspective of an entire public health system, survival has improved and HF hospitalizations have decreased after CRT implantation over the past decade. This prognostic improvement has occurred despite an increasing comorbidity burden.

* Corresponding author: Tel: +44 121 371 2000, *E-mail address*: cardiologists@hotmail.com

Graphical Abstract



In this study of all first cardiac resynchronization therapy (CRT) implantations undertaken in England (left-side panels), there was an increase in comorbidities from 2010 to 2019 (right upper panel). In parallel, there was a reduction in the composite endpoint of total mortality or heart failure (HF) hospitalization (right lower panel). CKD, chronic kidney disease; CCI, Charlson comorbidity index; CRT-D, cardiac resynchronization therapy defibrillation; CRT-P, cardiac resynchronization-pacing.

Keywords Cardiac resynchronization therapy • Mortality • Heart failure hospitalization

What's new?

- Over the past decade, survival has improved and heart failure (HF) hospitalizations have decreased after cardiac resynchronization therapy (CRT) implantation.
- Over the same time period, comorbidities have increased, suggesting that the typical CRT patient in 2019 is more complex than in 2010.
- Improved outcomes after CRT have occurred despite an increasing comorbidity burden.

Introduction

Since its development in the 1990s, randomized, controlled trials (RCTs) have shown that cardiac resynchronization therapy (CRT) is an effective treatment for selected patients with heart failure (HF) and a wide QRS complex, by improving survival and reducing HF hospitalizations.[1] Whilst RCTs are crucial in modern medical practice, their generalizability to the 'real world' has become a focus for regulators and policy-makers.[2,3] In this respect, the Food and Drug Administration (FDA) considers that whilst RCTs are central in 'establishing a baseline for device performance', the findings of RCTs should be generalizable to the 'real world'.[4] This view has been echoed by European policy-makers.[5]

Numerous national and international registries[6,7] as well as administrative data sets have shown that CRT is deliverable in most cardiac centres. Such data sets, however, are limited to patients selected by participating centres and do not address long-term outcomes. Crucially, they do not throw light on the effects of CRT from the perspective of non-participating centres or an entire healthcare system.

With the rising demands and financial costs of CRT,[8] we may ask whether clinical outcomes have improved. In this context, we explored clinical outcomes after CRT implantation over the past decade in the context of an entire public healthcare system.

Methods

This is a retrospective study of consecutive patients undergoing CRT-pacing (CRT-P) or CRT-defibrillation (CRT-D) device implantation in England,

from 1 January 2010 to 31 December 2019, with follow-up until 31 March 2021. We used the National Health Service Hospital Episode Statistics (HES) data sets, provided by the National Health Service Digital to University Hospitals Birmingham under a data sharing agreement. Pursuance of Section 251 of the National Health Service Act 2006 waived the need for Ethics Committee approval and patient consent. The HES data warehouse comprises all National Health Service hospitals in England (56.3 M population in 2019). Linking using a pseudo patient identifier permitted analyses of patient-level data in the whole territory of England, and therefore, any hospital event in the country was captured. Episodes of care for the different diagnoses were identified using International Classification of Diseases 10th revision (ICD-10) codes and the Office of Population, Censuses and Surveys Classification of Interventions and Procedures version 4 (see Supplementary material online, *Table S1*, and Appendix). Survival status and date of death was checked against the Office of National Statistics. The study was approved by the Clinical Audit and Informatics Departments, University Hospitals Birmingham, Queen Elizabeth.

The study period 2010–2019 was chosen because coding of CRT through the National Tariff was unreliable prior to 2010, when coding procedures were standardized following implementation of the 'payment by results' policy. Patients receiving a conventional pacemaker or an implantable cardioverter–defibrillator without CRT were excluded. (*Figure 1*).

Endpoints

The primary endpoint was total mortality. The secondary endpoint was total mortality or hospitalization for HF, whichever occurred first. A first diagnosis of HF in the dominant episode during the hospital spell was considered as a HF hospitalization. The ancillary endpoint was HF hospitalization.

Comorbidities

Patients were regarded as having a history of hypertension, diabetes mellitus, chronic kidney disease, or myocardial infarction if these diagnoses appeared in any hospital spell at any time before CRT device implantation, according to coding dating back to 2005. The Charlson comorbidity index[9] (CCI) was used as a measure of comorbidity, quantified using diagnoses at the same hospital spell when CRT device implantation was undertaken.

Aetiology

As the underlying aetiology of cardiomyopathy was not specifically coded, we categorized aetiology as ischaemic if there was a previous coded diagnosis of angina pectoris, acute myocardial infarction, other acute ischaemic heart diseases, and chronic ischaemic heart disease (see Supplementary material online, *Table S1*, and *Appendix*).

Statistical analysis

Continuous variables are expressed as mean (±SD) and compared using Student's *t*-test. Categorical variables were compared using the χ^2 statistic. Kaplan–Meier curves and the logrank test were used to assess differences in cumulative survival. Cox proportional hazard models were used to compare risks across subgroups. Proportionality hypotheses were first verified by visual examination of log (survival) graphs to ensure parallel slopes and by examining Schoenfeld residuals. Data were censored at the date of death/HF hospitalization or the end of the follow-up period. A two-sided

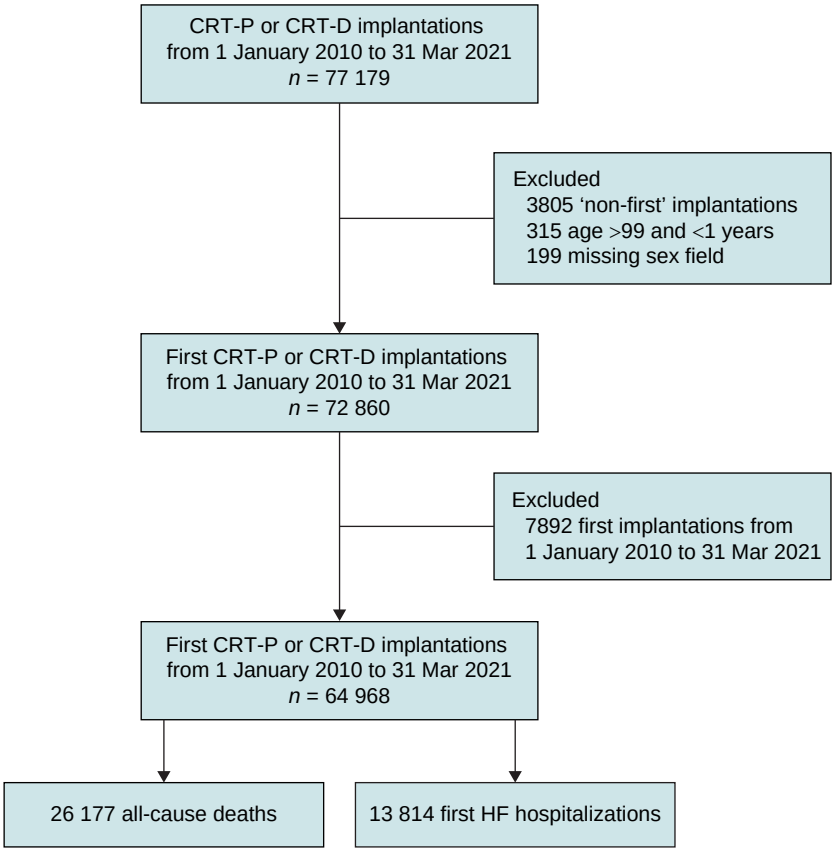


Figure 1 Derivation of the study cohort. CRT-P, cardiac resynchronization therapy-pacemaker; CRTD, cardiac resynchronization therapy-defibrillator.

$P \leq 0.05$ was considered statistically significant. Statistical analyses were undertaken using Stata 15 (StataCorp, Texas).

Results

In the period 2010–2019, 64 968 consecutive patients [age 71.4 ± 11.7 years; 48 606 (74.8%) male] underwent CRT-D [$n = 32\,313$ (49.7%)] or CRT-P [$n = 32\,655$ (50.3%)] device implantation (*Figure 1*). There was a 76% increase in CRT implantations from 4257 in 2010 to 7494 in 2019 (*Table 1* and *Figure 2*). In the whole cohort, most patients were white (84.9%) and 22.3% had a CCI ≥ 3.

Total mortality

Over a median follow-up of 4.54 years (interquartile range: 2.80–6.71) (272 989 person-years), 26 177 (40.3%) patients died. As shown in *Table 2*, total mortality progressively decreased at 30 days and 1 year. Crude 2 year total mortality rates decreased from 18.4% in 2010 to 14.2% in 2019 [univariate HR: 0.91; 95% confidence interval (CI) 0.87–0.96] (*Table 3*). Yearly figures are shown in Supplementary material online, *Table S2* (see Supplementary material online, *Appendix*).

In multivariable analyses, total mortality decreased from 2010–2011 to 2018–2019, after adjustment for age, race, sex, and comorbidities, including hypertension, diabetes, chronic kidney disease, and myocardial infarction (HR: 0.72; 95% CI 0.69–0.76) (Model 1, *Table 4*). This remained significant after correction for the CCI (HR: 0.81; 95% CI 0.77–0.85) (Model 2, *Table 4*).

Heart failure hospitalizations

Over the follow-up period, a total of 15 539 HF hospitalizations occurred any time after CRT implantation, of which 13 814 were first HF hospitalizations. Crude 2 year total mortality or HF hospitalizations decreased from 26.8% in 2010–2011 to 19.9% in 2018–2019 (univariate HR: 0.73; 95% CI 0.70–0.76) (*Tables 2* and *3* and *Figure 3*). Yearly figures are shown in Supplementary material online, *Table S3* (see Supplementary material online, *Appendix*).

In multivariable analyses, total mortality or HF hospitalizations decreased from 2010–2011 to 2018–2019, after adjustment for age, race, sex, and comorbidities, including hypertension, diabetes, chronic kidney disease, and myocardial infarction (HR: 0.59; 95% CI 0.57–0.62) (Model 1, *Table 4*). This remained significant after correction for the CCI (HR: 0.66; 95% CI 0.64–0.69) (Model 2, *Table 4*).

Comorbidity

After excluding patients with missing CCI values ($n = 10$), the proportion of patients with a CCI ≥ 3 increased from 20% in 2010–2011 to 25.1% in 2018–2019 (*Table 1* and *Figure 4*). The proportion of patients with hypertension, diabetes, chronic kidney disease, and myocardial infarction also increased (all $P < 0.001$). Survival curves according to the CCI are shown in *Figure 5*. In both univariate (*Table 3*) and multivariable

Table 1 Characteristics of the study group

N	All 64 968	2010–2011 9169	2012–2013 11 075	2014–2015 14 247	2016–2017 15 520	2018–2019 14 957	*P*
CRT-D	32 313 (49.7)	4082 (44.5)	5187 (46.8)	7927 (55.6)	8100 (52.2)	7017 (46.9)	<0.001
CRT-P	32 655 (50.3)	5087 (55.5)	5888 (53.2)	6320 (44.4)	7422 (47.8)	7938 (53.1)	
Sex (male)	48 606 (74.8)	6928 (75.6)	8343 (75.3)	10 703 (75.1)	11 464 (73.9)	11 168 (74.7)	0.014
Age	71.4 ± 11.7	70.2 ± 11.8	70.9 ± 11.6	71.5 ± 11.6	71.8 ± 11.6	72.1 ± 11.8	
< 70	9286 (14.3)	1446 (15.8)	1649 (14.9)	2004 (14.1)	2149 (13.9)	2038 (13.6)	<0.001
70–79	14 251 (21.9)	2173 (23.7)	2558 (23.1)	3254 (22.8)	3312 (21.3)	2954 (19.8)	
80–89	24 849 (38.3)	3650 (39.8)	4271 (38.6)	5367 (37.7)	5867 (37.8)	5694 (38.1)	
≥ 90	16 582 (25.5)	1900 (20.7)	2597 (23.5)	3622 (25.4)	4192 (27.0)	4271 (28.6)	
Race							
White	55 169 (84.9)	7987 (87.1)	9727 (87.8)	12 136 (85.2)	13 029 (84)	12 290 (82.2)	<0.001
Black or mixed black	998 (1.54)	147 (1.6)	169 (1.53)	239 (1.68)	217 (1.40)	226 (1.51)	
Asian or Asian British	2398 (3.69)	357 (3.89)	410 (3.70)	576 (4.04)	532 (3.43)	523 (3.50)	
Unknown	6403 (9.86)	678 (7.39)	769 (6.94)	1296 (9.10)	1742 (11.2)	1918 (12.8)	
Charlson comorbidity index							
0	16 504 (25.4)	2402 (26.2)	2780 (25.1)	3649 (25.6)	4008 (25.8)	3665 (24.5)	<0.001
1	20 315 (31.3)	2995 (32.7)	3495 (31.6)	4490 (31.5)	4837 (31.2)	4498 (30.1)	
2	13 658 (21.0)	1940 (21.2)	2360 (21.3)	3045 (21.4)	3267 (21.1)	3046 (20.4)	
≥ 3	14 481 (22.3)	1829 (20.0)	2434 (22.0)	3063 (21.5)	3408 (22.0)	3747 (25.1)	
Ischaemic aetiology	44 181 (68.0)	6343 (69.2)	7751 (70.0)	9748 (68.4)	10 499 (67.7)	9840 (65.8)	<0.001
Previous history							
Hypertension	44 917 (69.1)	5466 (59.6)	7379 (66.6)	9953 (69.9)	11 136 (71.8)	10 983 (73.4)	<0.001
Diabetes	18 865 (29.0)	2430 (26.5)	3019 (27.3)	4178 (29.3)	4632 (29.9)	4606 (30.8)	<0.001
Chronic kidney disease	11 574 (17.8)	790 (8.62)	1607 (14.5)	2724 (19.1)	3094 (19.9)	3359 (22.5)	<0.001
Myocardial infarction	12 123 (18.7)	1442 (15.7)	2016 (18.2)	2627 (18.4)	3129 (20.2)	2909 (19.5)	<0.001

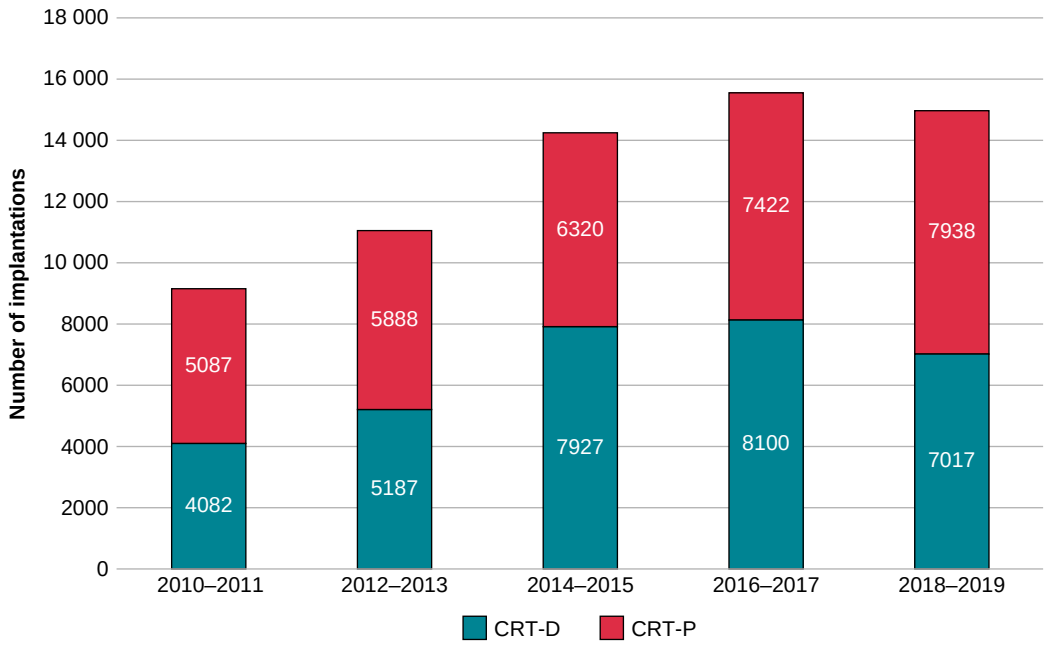


Figure 2 Temporal trends in CRT-P and CRT-D implantation. Absolute number of implantations in England from 2010 to 2019 are shown, grouped into 2 year periods. A significant increase was observed over the decade ($P < 0.001$). CRT-P, cardiac resynchronization therapy-pacemaker; CRTD, cardiac resynchronization therapy-defibrillator.

Table 2 Total mortality and heart failure hospitalizations

Year groups	2010–2011	2012–2013	2014–2015	2016–2017	2018–2019	*P*	Total
Number of patients	9169	11 075	14 247	15 520	14 957	< 0.001	64 968
Total mortality							
30 days							
Alive	9038	10 923	14 088	15 370	14 794	< 0.001	64 213
Total mortality	131	152	159	150	163		755
Total mortality (%)	1.43	1.37	1.12	0.97	1.09		1.16
1 year							
Alive	8220	10 022	12 954	14 185	13 741	< 0.001	59 122
Total mortality	949	1053	1293	1335	1216		5846
Total mortality (%)	10.35	9.51	9.08	8.6	8.13		9
Total mortality or HF hospitalization							
30 days							
Alive	8849	10 743	13 860	15 147	14 586	< 0.001	63 185
Total mortality or HF hospitalization	320	332	387	373	371		1783
Total mortality or HF hospitalization (%)	3.49	3	2.72	2.4	2.48		2.74
1 year							
Alive	7546	9256	12 098	13 201	12 927	< 0.001	55 028
Total mortality or HF hospitalization	1623	1819	2149	2319	2030		9940
Total mortality or HF hospitalization (%)	17.7	16.42	15.08	14.94	13.57		15.3
HF hospitalization							

Continued

Table 2 *Continued*

Year groups	2010–2011	2012–2013	2014–2015	2016–2017	2018–2019	*P*	Total
30 days							
Alive	8966	10 878	14 001	15 279	14 738	< 0.001	63 862
HF hospitalization	203	197	246	241	219		1106
HF hospitalization (%)	2.21	1.78	1.73	1.55	1.46		1.7
1 year							
Alive	8179	9959	12 993	14 107	13 827	< 0.001	59 065
HF hospitalization	990	1116	1254	1413	1130		5903
HF hospitalization (%)	10.8	10.08	8.8	9.1	7.55		9.09

Table 3 Univariate analyses

	Total mortality				Total mortality or HF hospitalization				HF hospitalization			
	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*
CRT-D	0.74	0.72	0.75	<0.001	0.81	0.79	0.82	<0.001	1.03	1.00	1.07	0.063
Sex (male)	1.45	1.40	1.49	<0.001	1.37	1.33	1.41	<0.001	1.32	1.27	1.38	<0.001
Age												
< 60												
60–69	1.77	1.68	1.87	<0.001	1.42	1.35	1.48	<0.001	1.13	1.07	1.20	<0.001
70–79	2.79	2.65	2.93	<0.001	1.98	1.90	2.07	<0.001	1.26	1.19	1.33	<0.001
≥ 80	4.77	4.53	5.02	<0.001	3.07	2.94	3.20	<0.001	1.50	1.42	1.59	<0.001
Race[a]												
White												
Black or mixed black	0.93	0.84	1.03	0.176	1.13	1.03	1.23	0.007	1.59	1.42	1.78	<0.001
Asian or Asian British	0.92	0.86	0.98	0.009	1.05	0.99	1.11	0.105	1.43	1.32	1.54	<0.001
Unknown	0.84	0.80	0.88	<0.001	0.84	0.80	0.87	<0.001	0.88	0.83	0.93	<0.001
Charlson comorbidity index[b]												
1	1.25	1.21	1.30	<0.001	1.25	1.21	1.29	<0.001	1.27	1.21	1.33	<0.001
2	1.70	1.64	1.77	<0.001	1.66	1.60	1.72	<0.001	1.66	1.57	1.74	<0.001
≥ 3	2.69	2.60	2.79	<0.001	2.54	2.46	2.62	<0.001	2.37	2.26	2.49	<0.001
Ischaemic aetiology	1.67	1.62	1.71	<0.001	1.65	1.61	1.70	<0.001	1.73	1.67	1.80	<0.001
Previous history												
Hypertension	1.62	1.57	1.66	<0.001	1.57	1.53	1.61	<0.001	1.50	1.45	1.56	<0.001
Diabetes	1.55	1.51	1.59	<0.001	1.57	1.53	1.61	<0.001	1.64	1.59	1.70	<0.001
Chronic kidney disease	2.43	2.37	2.50	<0.001	2.26	2.20	2.32	<0.001	2.06	1.98	2.14	<0.001
Myocardial infarction	1.45	1.41	1.49	<0.001	1.46	1.42	1.50	<0.001	1.49	1.43	1.55	<0.001
Year												
2010–2011												
2012–2013	0.98	0.94	1.01	0.209	0.94	0.90	0.97	<0.001	0.87	0.82	0.91	<0.001
2014–2015	0.95	0.91	0.98	0.003	0.87	0.84	0.90	<0.001	0.74	0.70	0.77	<0.001
2016–2017	0.91	0.88	0.95	<0.001	0.82	0.79	0.85	<0.001	0.66	0.63	0.70	<0.001
2018–2019	0.91	0.87	0.96	<0.001	0.73	0.70	0.76	<0.001	0.47	0.44	0.50	<0.001

Results are expressed as hazard ratios and 95% CI.
[a]Compared with white race.
[b]Comparison with a CCI of 0.

Table 4 Multivariable analyses

	Total mortality				Total mortality or HF hospitalization				HF Hospitalization			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Model 1												
CRT-D	0.91	0.89	0.93	<0.001	0.93	0.91	0.96	<0.001	1.06	1.03	1.10	0.001
Sex (male)	1.43	1.39	1.48	<0.001	1.33	1.29	1.36	<0.001	1.23	1.18	1.29	<0.001
Age (years)	1.05	1.05	1.05	<0.001	1.03	1.03	1.03	<0.001	1.01	1.01	1.01	<0.001
Race (white)	1.08	1.04	1.12	<0.001	1.03	0.99	1.06	0.113	0.90	0.86	0.95	<0.001
Previous history												
Hypertension	1.14	1.10	1.17	<0.001	1.17	1.14	1.20	<0.001	1.25	1.20	1.30	<0.001
Diabetes	1.35	1.31	1.38	<0.001	1.35	1.32	1.39	<0.001	1.39	1.34	1.44	<0.001
Chronic kidney disease	1.86	1.81	1.92	<0.001	1.83	1.78	1.88	<0.001	1.90	1.83	1.98	<0.001
Myocardial infarction	1.27	1.23	1.31	<0.001	1.29	1.25	1.32	<0.001	1.30	1.24	1.35	<0.001
Year												
2010–2011												
2012–2013	0.89	0.86	0.93	<0.001	0.87	0.84	0.90	<0.001	0.81	0.77	0.85	<0.001
2014–2015	0.81	0.78	0.84	<0.001	0.75	0.72	0.78	<0.001	0.64	0.61	0.67	<0.001
2016–2017	0.75	0.72	0.78	<0.001	0.69	0.67	0.72	<0.001	0.57	0.54	0.60	<0.001
2018–2019	0.72	0.69	0.76	<0.001	0.59	0.57	0.62	<0.001	0.39	0.37	0.42	<0.001
Model 2												
CRT-D	0.90	0.87	0.92	<0.001	0.92	0.90	0.95	<0.001	1.06	1.02	1.09	0.003
Sex (male)	1.41	1.37	1.46	<0.001	1.31	1.28	1.35	<0.001	1.23	1.18	1.28	<0.001
Age (years)	1.05	1.05	1.05	<0.001	1.03	1.03	1.03	<0.001	1.01	1.01	1.01	<0.001
Race (white)	1.06	1.02	1.09	0.003	1.01	0.98	1.04	0.533	0.88	0.84	0.93	<0.001
Charlson comorbidity index[a]												
1	1.20	1.16	1.25	<0.001	1.20	1.16	1.24	<0.001	1.23	1.17	1.29	<0.001
2	1.55	1.49	1.61	<0.001	1.53	1.48	1.58	<0.001	1.58	1.50	1.66	<0.001
≥ 3	2.25	2.17	2.33	<0.001	2.20	2.13	2.28	<0.001	2.24	2.13	2.36	<0.001
Year												
2010–2011												
2012–2013	0.93	0.90	0.97	<0.001	0.90	0.87	0.94	<0.001	0.85	0.81	0.89	<0.001
2014–2015	0.89	0.86	0.92	<0.001	0.83	0.80	0.85	<0.001	0.71	0.68	0.75	<0.001
2016–2017	0.85	0.81	0.88	<0.001	0.78	0.75	0.81	<0.001	0.64	0.61	0.68	<0.001
2018–2019	0.81	0.77	0.85	<0.001	0.66	0.64	0.69	<0.001	0.44	0.41	0.47	<0.001

Results are expressed as hazard ratios and 95% CI.
[a]Comparison with a CCI of 0.

(*Table 4*) analyses, an increasing CCI was associated with an increased risk of the three endpoints. As noted above, a reduction in the risk of the three endpoints occurred despite an increasing comorbidity burden.

Discussion

This is the first study to explore temporal trends in clinical outcomes after CRT from the perspective of an entire public healthcare system. Several findings have emerged (Graphical Abstract). First, the number of CRT implantations increased by 76% from 2010 to 2019. Second, total mortality after CRT decreased. Third, the composite endpoint of total mortality or HF hospitalizations as well as HF hospitalizations *per se* also decreased. Fourth, age, male sex, white race, ischaemic aetiology, chronic kidney disease, diabetes mellitus, and hypertension as well as an increasing CCI were associated with worse outcomes. Last, despite this, the reduction in total mortality and HF hospitalizations over the years occurred despite an increasing comorbidity burden.

Total mortality and heart failure hospitalizations

From a clinician's and a healthcare system's perspective, it is crucial to ascertain whether increased delivery of a therapy translates to improved patient-related outcomes in the 'real-world'.[4] Few national and international registries have provided data on the clinical outcomes after CRT. Whilst the European Society of Cardiology CRT registries

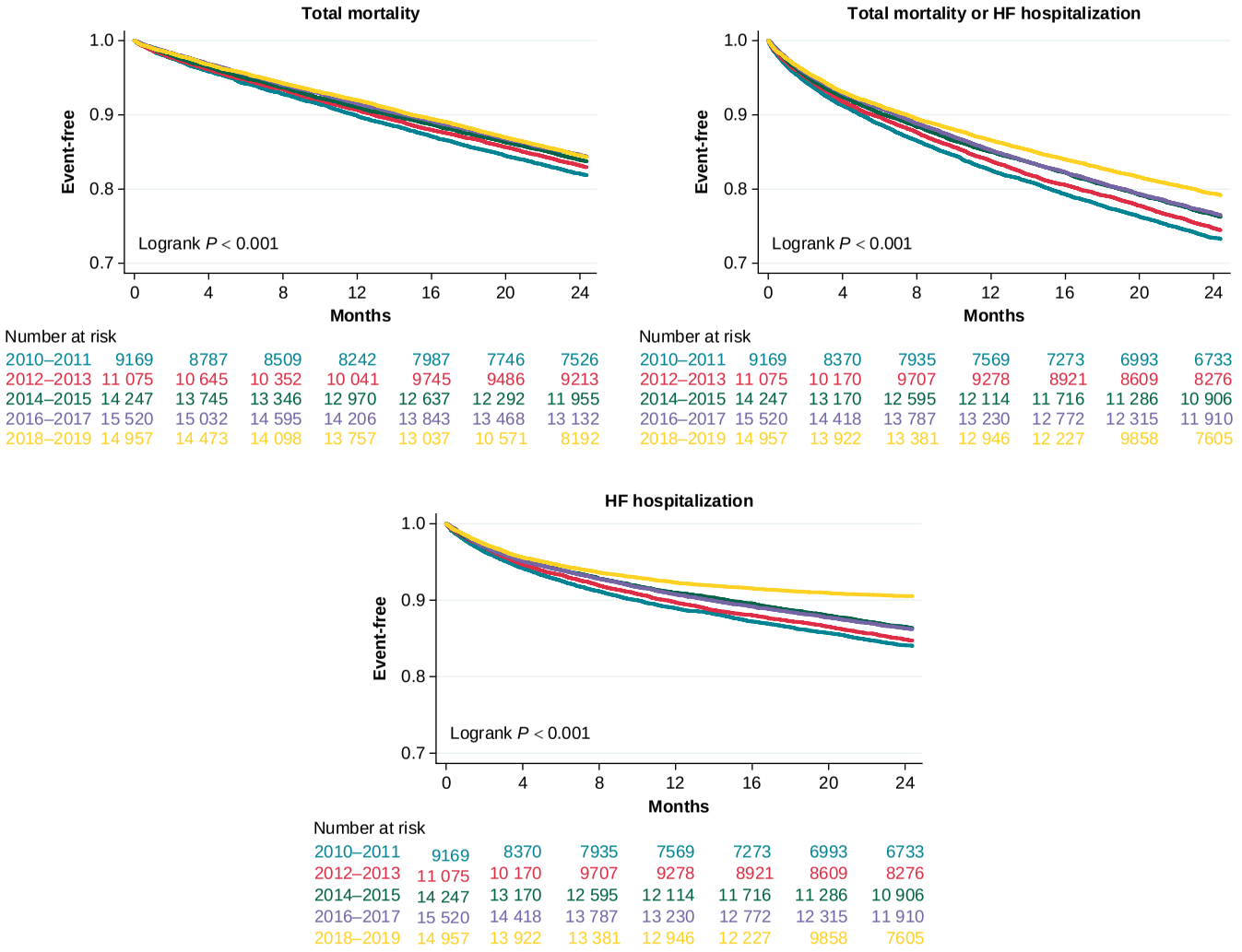


Figure 3 Survival curves: temporal trends. Graphs show Kaplan–Meier survival curves for the three endpoints, according to 2 year cohorts.

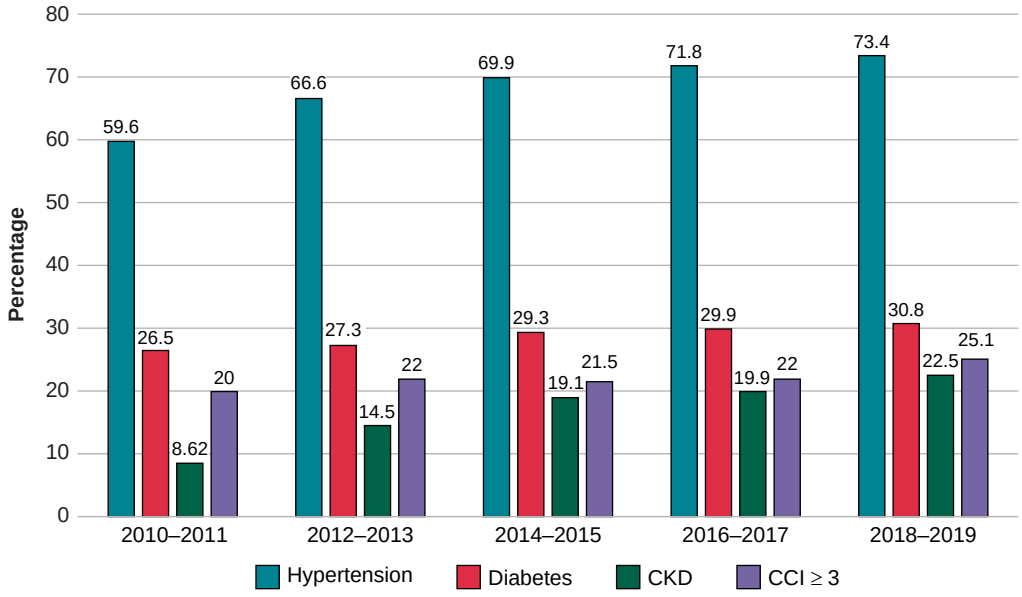


Figure 4 Progression of comorbidities over time. The histograms show the proportion of patients with hypertension, diabetes mellitus, and chronic kidney disease (CKD) over the study period. CCI, Charlson comorbidity index.

provide invaluable, benchmarking data on CRT practice,[10] they do not address clinical outcomes. In the USA, the National Cardiovascular Data Registry of Medicare beneficiaries showed that among 53 174 CRT-D recipients, crude, 2 year total mortality decreased from 21.7% in 2011 to 16.9% in 2015.[6] Notwithstanding the limitations of registries, including selection bias, these figures are comparable to ours (18.2% in 2010–2011, 16.3% in 2014–2015%, and 14.7% in 2018–2019).

As well as an improvement in survival, we found a reduction in the composite endpoint of total mortality or HF hospitalization over the decade. This reduction was driven by reductions in both total mortality and HF hospitalizations. Compared with those by 2010–2011, HF hospitalizations by 2018–2019 decreased by 61% after co-variate adjustment. As with other endpoints, this reduction occurred despite a rising comorbidity burden. A notable finding was the pronounced reduction on HF hospitalizations observed after 2018.

One may ask whether improved survival is attributable to CRT *per se*. In this respect, CRT device implantation has remained almost unchanged since its introduction in the early 1990s. The use of quadripolar left ventricular leads has been linked to better outcomes,[11,12] but no other 'game-changing' technological advances have occurred. On the other hand, improved outcomes may relate to drug treatment of HF. In this respect, sacubitril/valsartan emerged in 2014,[13] but penetration into clinical practice in the UK did not occur until 2020. Likewise, this study was undertaken prior to the emergence of the use of sodium–glucose co-transporter-2 inhibitors in HF. We cannot discount the possibility that increased penetration of HF medications and earlier delivery of CRT[14] over the years may have contributed. The formalization of the care of patients with HF[15] and CRT[16,17] over the past decade may also be relevant.

Comorbidities

Manifold observational studies have shown that comorbidities have a major impact on clinical outcomes in patients with HF[18,19] and after device therapy.[20,21] In a study of 463 CRT-D recipients, an age-adjusted CCI ≥ 5 had more than a three-fold increase in total mortality.[21] In another study, each tertile of Charlson age-adjusted comorbidity index was independently associated with a 37% higher total mortality after CRT.[22] We found that, over the years, CRT recipients were older and more likely to have pre-existing conditions, including hypertension, diabetes, and chronic kidney disease. Moreover, there was an increasing comorbidity burden over time, quantified using the CCI. This suggests that the CRT patient population has changed. Importantly, however, survival after CRT improved over the years, regardless of an increasing comorbidity burden.

We should consider that the CCI, developed in 1987 in a study of 559 medical patients,[9] is a very broad and perhaps outdated measure of comorbidity, particularly with regard to the weighting applied to its constituent risk factors. For example, congestive HF, acute myocardial infarction, and peptic ulcer disease attract the same weighting of 1, whilst the acquired immunodeficiency syndrome has a weighting of 6. This adjudicated equivalence in risk is difficult to accept in current medicine. Notwithstanding these limitations, the use of CCI in our data set does provide the empirical signal that comorbidities impact on clinical outcomes after CRT.

Limitations

This study has all the limitations of retrospective, observational studies based on administrative data sets. Whilst rich in numbers, clinical details are limited. We have no data on left ventricular function, electrocardiogram (ECG) variables, or medications, all of which are known to impact on clinical outcomes. Whilst establishing that outcomes after CRT have improved, we cannot throw light on possible causes, prominent amongst which are developments in HF treatments other than device therapy, and, in addition, nor can we exclude the possibility that improved treatment of comorbidities was also at play. Because the aetiology of cardiomyopathy is not specifically coded in this database, we assumed that the underlying aetiology of HF in CRT recipients was ischaemic cardiomyopathy if there was previous coding of coronary artery disease. This definition may yield a higher proportion of ischaemic cardiomyopathy, compared with other cohorts. Adjustment for

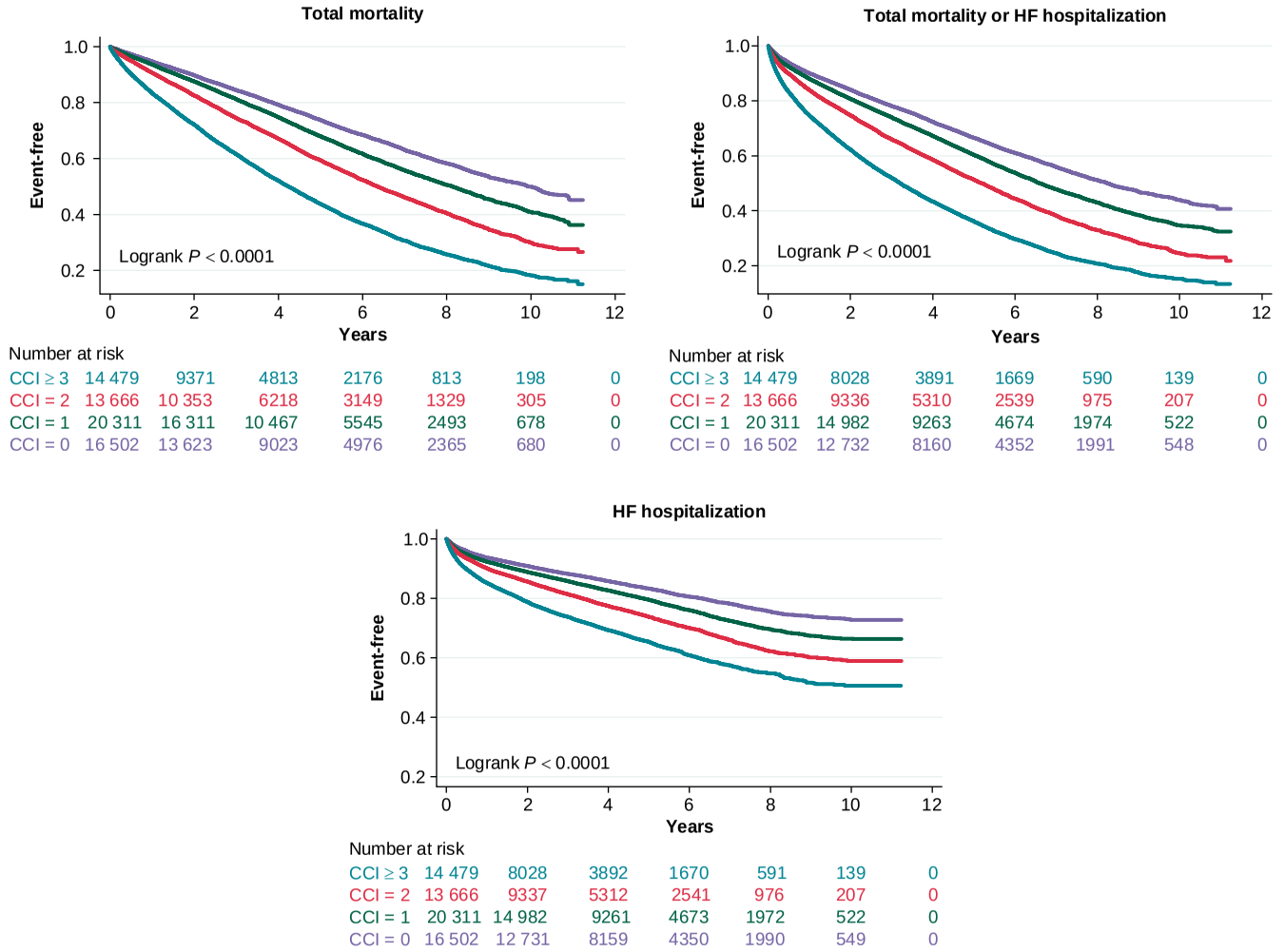


Figure 5 Survival curves: effect of comorbidities. Graphs show Kaplan–Meier survival curves for the three endpoints in the entire cohort, grouped according to the Charlson comorbidity index (CCI). CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator.

comorbidities and other factors included herein cannot not replace randomization.

Conclusions

From the perspective of an entire national healthcare system, total mortality and HF hospitalizations after CRT have decreased over the past decade. This prognostic improvement has occurred despite an older population and a higher comorbidity burden.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: F.L. is a consultant to and has received financial research support from Medtronic, Abbott, Boston Scientific, Biotronik, and Microport. A.Z. receives research funding from Medtronic. Other authors report no conflicts of interest.

Data availability

Sharing of the original data will require a data sharing agreement. Summary data can be provided at reasonable request.

References

1. Leyva F, Nisam S, Auricchio A. 20 years of cardiac resynchronization therapy. *J Am Coll Cardiol* 2014;**64**:1047–58.
2. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL *et al.* Real-world evidence—what is it and what can it tell us? *N Eng J Med* 2016;**375**:2293–7.
3. Jarow JP, LaVange L, Woodcock J. Multidimensional evidence generation and FDA regulatory decision making: defining and using "real-world" data. *JAMA* 2017;**318**:703–4.
4. US Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices. Guidance for Industry and Food and Drug Administration Staff. In: Administration USDoHaHSFaD, ed. Rockville: U.S. Department of Health and Human Services Food and Drug Administration 2017.
5. National Institute for Health and Care Excellence. NICE real-world evidence frameworkLondon 2022.
6. Darden D, Peterson P, Xin X, Munir M, Minges K, Goldenberg I *et al.* Temporal trends and long-term outcomes among recipients of cardiac resynchronization therapy with defibrillator in the United States, 2011–2015: insights from the National Cardiovascular Data Registry. *Heart Rhythm O2* 2022;**3**:405–14.
7. Arribas F, Auricchio A, Wolpert C, Merkely B, Merino JL, Boriani G *et al.* The EHRA white book. *Europace* 2012;**14**:ii1–ii55.
8. Varma N, Auricchio A, Connolly AT, Boehmer J, Bahu M, Costanzo MR *et al.* The cost of non-response to cardiac resynchronization therapy: characterizing heart failure events following cardiac resynchronization therapy. *Europace* 2021;**23**:1586–95.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.
10. Dickstein K, Normand C, Auricchio A, Bogale N, Cleland JG, Gitt AK *et al.* CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients-who is doing what to whom and how? *Eur J Heart Fail* 2018;**20**:1039–51.
11. Leyva F, Zegard A, Qiu T, Acquaye E, Ferrante G, Walton J *et al.* Cardiac resynchronization therapy using quadripolar versus non-quadripolar left ventricular leads programmed to biventricular pacing with single-site left ventricular pacing: impact on survival and heart failure hospitalization. *J Am Heart Assoc* 2017;**6**:e007026.
12. Erath JW, Benz AP, Hohnloser SH, Vamos M. Clinical outcomes after implantation of quadripolar compared to bipolar left ventricular leads in patients undergoing cardiac resynchronization therapy: a systematic review and meta-analysis. *Europace* 2019;**21**:1543–9.
13. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR *et al.* Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Eng J Med* 2014;**371**:993–1004.
14. Leyva F, Zegard A, Patel P, Stegemann B, Marshall H, Ludman P *et al.* Timing of cardiac resynchronization therapy implantation. *Europace* 2023:1–10.
15. Cleland JGF, McDonagh T, Rigby AS, Yassin A, Whittaker T, Dargie HJ. The national heart failure audit for England and Wales 2008-2009. *Heart* 2011;**97**:876–86.
16. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA *et al.* 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118.
17. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM *et al.* 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace* 2022;**24**:71–164.
18. Thibodeau JB, Pillarisetti J, Khumri TM, Jones PG, Main ML. Mortality rates and clinical predictors of reduced survival after cardioverter defibrillator implantation. *Am J Cardiol* 2008;**101**:861–4.
19. Jong P, Gong Y, Liu PP, Austin PC, Lee DS, Tu JV. Care and outcomes of patients newly hospitalized for heart failure in the community treated by cardiologists compared with other specialists. *Circulation* 2003;**108**:184–91.
20. Leyva F, Zegard A, Okafor O, de Bono J, McNulty D, Ahmed A *et al.* Survival after cardiac resynchronization therapy: results from 50 084 implantations. *Europace* 2019;**21**:754–62.
21. Theuns DA, Schaer BA, Soliman OI, Altmann D, Sticherling C, Geleijnse ML *et al.* The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: comorbidity burden as predictor of mortality. *Europace* 2011;**13**:62–9.
22. Ioannou A, Papageorgiou N, Barber H, Falconer D, Barra S, Babu G *et al.* Impact of an age-adjusted co-morbidity index on survival of patients with heart failure implanted with cardiac resynchronization therapy devices. *Am J Cardiol* 2017;**120**:1158–65.