ESC European Society of Cardiology

Europace (2023) **25**, 1–10
https://doi.org/10.1093/europace/euad059

CLINICAL RESEARCH

Timing of cardiac resynchronization therapy implantation

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

[1]Aston Medical Research Institute, Aston University, Aston Triangle, Birmingham B4 7ET, UK; [2]Department of Cardiology, University Hospitals Birmingham, Queen Elizabeth, Mindelsohn Way, Birmingham B15 2GW, UK; and [3]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Via Università, 4, 41121, Modena, Italy

Received 2 December 2022; accepted after revision 14 February 2023

Aims The optimum timing of cardiac resynchronization therapy (CRT) implantation is unknown. We explored long-term outcomes after CRT in relation to the time interval from a first heart failure hospitalization (HFH) to device implantation.

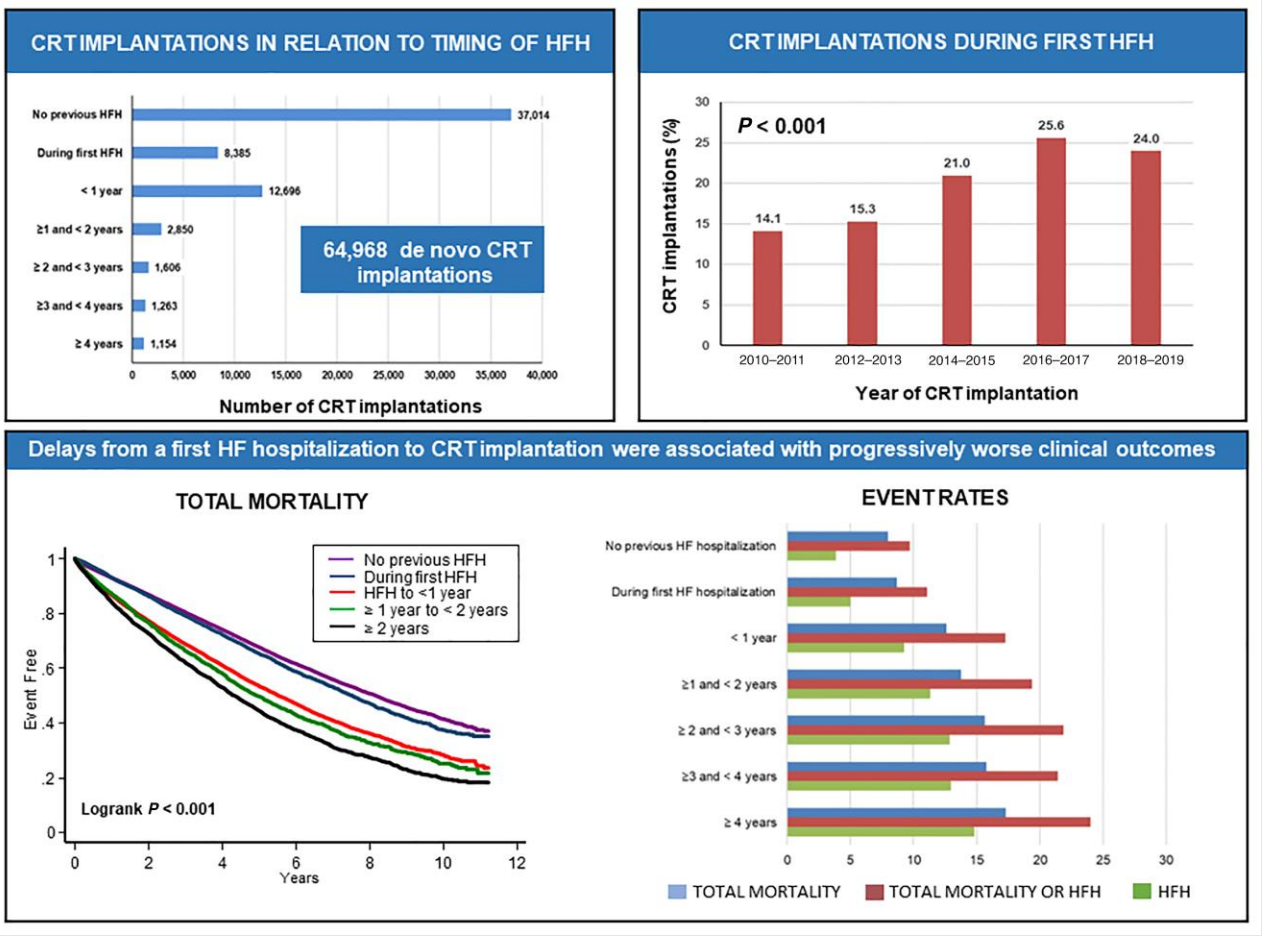
Methods and results A database covering the population of England (56.3 million in 2019) was used to quantify clinical outcomes after CRT implantation in relation to first HFHs. From 2010 to 2019, 64 968 patients [age: 71.4 ± 11.7 years; 48 606 (74.8%) male] underwent CRT implantation, 57% in the absence of a previous HFH, 12.9% during the first HFH, and 30.1% after ≥1 HFH. Over 4.54 (2.80–6.71) years [median (interquartile range); 272 989 person-years], the time in years from the first HFH to CRT implantation was associated with a higher risk of total mortality [hazard ratio (HR); 95% confidence intervals (95% CI)] (1.15; 95% CI 1.14–1.16, HFH (HR: 1.26; 95% CI 1.24–1.28), and the combined endpoint of total mortality or HFH (HR: 1.19; 95% CI 1.27–1.20) than CRT in patients with no previous HFHs, after co-variate adjustment. Total mortality (HR: 1.67), HFH (HR: 2.63), and total mortality or HFH (HR: 1.92) (all $P < 0.001$) were highest in patients undergoing CRT ≥2 years after the first HFH.

Conclusion In this study of a healthcare system covering an entire nation, delays from a first HFH to CRT implantation were associated with progressively worse long-term clinical outcomes. The best clinical outcomes were observed in patients with no previous HFH and in those undergoing CRT implantation during the first HFH.

Condensed abstract The optimum timing of CRT implantation is unknown. In this study of 64 968 consecutive patients, delays from a first heart failure hospitalization (HFH) to CRT implantation were associated with progressively worse long-term clinical outcomes. Each year from a first HFH to CRT implantation was associated with a 21% higher risk of total mortality and a 34% higher risk of HFH. The best outcomes after CRT were observed in patients with no previous HFHs and in those undergoing implantation during their first HFH.

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

Graphical Abstract



The *left upper panel* shows the timing (*y*-axis) and numbers (*x*-axis) of cardiac resynchronization therapy (CRT) implantations in relation to the timing of first heart failure hospitalizations (HFHs); the *right upper panel* shows CRT implantations undertaken during a first HFH as a percentage of all implantations, according to year. Patients were regarded as not having had a HFH if this had not occurred within 5 years prior to CRT implantation. The *left lower panel* shows the Kaplan–Meier survival curve for total mortality. Event rates (per 100 person-years) for the three endpoints according to the timing of CRT implantation in relation to a first HFH are shown in the *right lower panel*.

Keywords Heart failure • Cardiac resynchronization therapy • Mortality • Heart failure hospitalization

What's new?

- The optimum timing of CRT implantation is unknown.
- In this study of a public healthcare system covering an entire nation, increasing time from a first heart failure hospitalization (HFH) to CRT implantation was associated with progressively worse outcomes, with each year amounting to a 21% higher mortality and a 34% higher risk of HFH.
- The best outcomes were observed in patients with no previous HFHs and in those undergoing implantation during the first HFH.

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for selected patients with heart failure (HF) and a wide QRS complex.[1] The timing of CRT implantation in relation to the time of diagnosis or a heart failure hospitalization (HFH) has not been addressed by randomized, controlled trials. Current guidelines recommend CRT implantation as an elective procedure, in the context of stable HF.[1,2]

Several small studies[3] and large registries[4,5] have suggested that CRT should be delivered soon after the detection of HF, even during a HFH. In this respect, a HFH is a critical event in the trajectory of HF and may provide the opportunity to target patients who are most likely to benefit from CRT. However, acute HF carries a high risk, possibly high enough to dilute long-term benefits. In practice, a substantial proportion of CRT implantations are undertaken during a HFH.[4,6,7]

In this study of a healthcare system covering the entire population of England, we explored long-term clinical outcomes after CRT implantation during the first HFH and at different time points thereafter.

Methods

This is a retrospective study of consecutive patients undergoing CRT-pacing (CRT-P) or CRT-defibrillation (CRT-D) implantation in the National Health

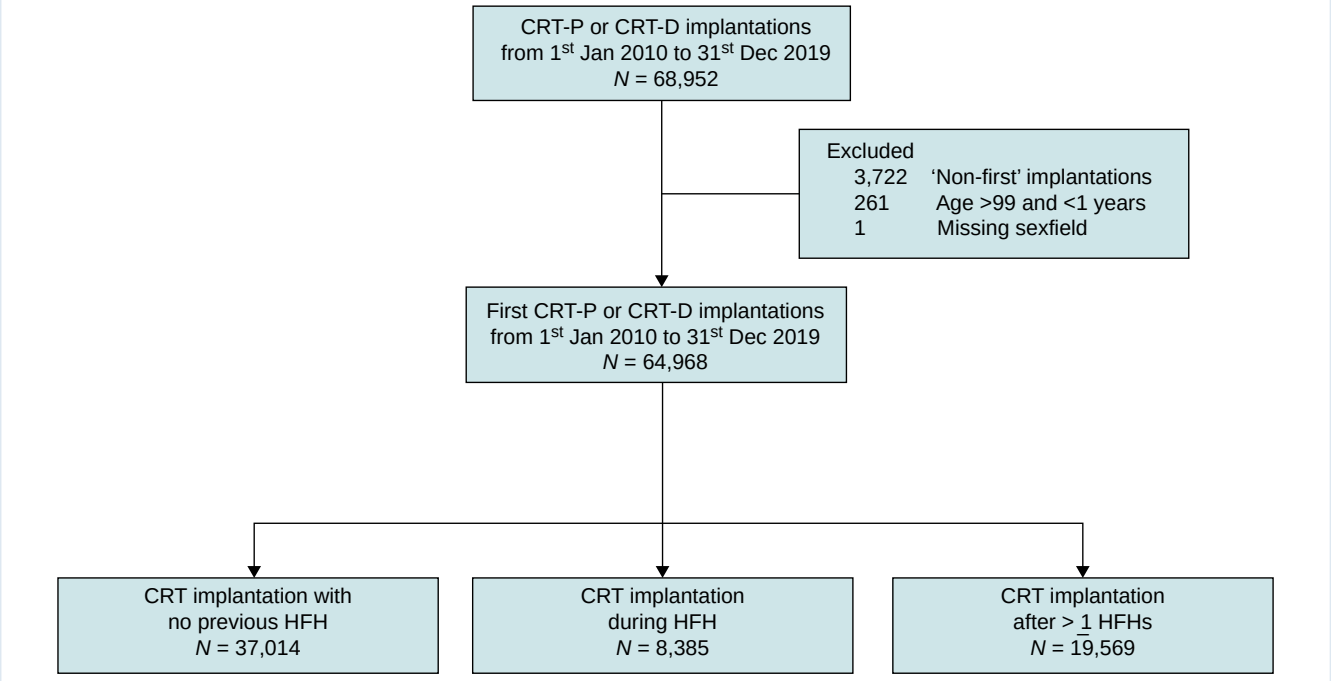


Figure 1 Derivation of the study cohort. CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator; HF, heart failure; HFH, heart failure hospitalization.

Service of England. This service provides comprehensive healthcare to the whole population of England (56.3 M in 2019), free of charge at the point of delivery. The National Health Service Hospital Episode Statistics is a data warehouse covering all inpatient and outpatient activity in all hospitals of the National Health Service. Our datasets were derived through a data sharing agreement, subject to Section 251 of the National Health Service Act 2006, which waives the need for ethics committee approval and patient consent.

The study period from 1 January 2010 to 31 December 2019, with follow-up until 31 March 2021, was chosen because coding of CRT through the National Tariff was unreliable prior to 2010, when it was standardized following the 'payment by results' national policy. Patients undergoing pacemaker or an implantable cardioverter defibrillator implantation without CRT were excluded (*Figure 1*). The International Classification of Diseases 10th revision (ICD-10) codes and the Office of Population, Censuses and Surveys Classification of Interventions and Procedures (OPCS) Version 4 were used in coding. Vital status and cause and date of death were cross-checked against the Office for National Statistics. The study was approved by the Clinical Audit Department, University Hospitals Birmingham, Queen Elizabeth.

Endpoints. Total mortality was the primary endpoint. The secondary endpoint was total mortality or hospitalization for HF, whichever occurred first. The ancillary endpoint was HFH. A hospitalization was considered as a HFH if a code for HF (ICD-10 codes I50.x) was dominant (in the first position). We considered that patients did not have a HFH if this had not occurred over a time window of 5 years prior to CRT implantation. A CRT implantation was considered as occurring during a HFH if the primary diagnosis for the hospitalization was HF and CRT implantation (OPCS code K596 for CRT-D and K607 or K617 for CRT-P; Supplementary material online, *Table S1, Appendix*) had occurred during the same hospitalization. The interval from a first HFH to CRT implantation related to the time difference from the date of admission to the first HFH to the date of CRT implantation.

Aetiology. The aetiology of cardiomyopathy was not specifically coded. We therefore categorized the aetiology as ischaemic if there was a previously coded diagnosis of coronary artery bypass, percutaneous coronary intervention, angina pectoris, acute myocardial infarction, other acute ischaemic heart diseases, or chronic ischaemic heart disease (see Supplementary material online, *Table S1, Appendix*).

Statistical analysis

Continuous variables are expressed as mean (±SD) and compared using the Student's *t*-test. Categorical variables were compared using the chi-squared 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/HFH or the end of the follow-up period. Timing of CRT implantation was examined in five ordinal groups as well as a continuous variable from a HFH to CRT implantation. In these analyses, patients with no HFHs were coded as zero, patients undergoing CRT implantation during the HFH were coded as 0.001, and the remainder were coded as the time in years from the first HFH to CRT implantation. A two-sided $P \leq 0.05$ was considered statistically significant. Statistical analyses were undertaken using Stata 15 (StataCorp, Texas).

Results

The derivation of the study group is shown in *Figure 1*. In the period 2010–19, 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%]) implantation. Most patients were white (84.9%). A history of hypertension was evident in 69.1%, and factors amounting to an underlying ischaemic aetiology were found in 68%. Comorbidities included diabetes mellitus (29%) and chronic kidney disease (17.8%). The majority (57%) had no previous HFH, 12.9% underwent CRT implantation during the first HFH, and 30.1% underwent CRT implantation after ≥1 HFHs (*Graphical Abstract*). The proportion of patients undergoing CRT implantation during the first HFH increased from 2010–11 to 2018–19 (14.1–24.0%, $P < 0.001$) (*Table 1*, Graphical Abstract). The time from a first HFH to CRT implantation was 6.9 (interquartile range: 1.73–19.6) months, with 42.8% of patients undergoing CRT implantation after ≥ 9 months.

Table 1 Characteristics of the study group

	Timing of CRT implantation after first HFH						
	All	**No previous HFH**	**During HFH**	**< 1 year**	**≥ 1 year and < 2 years**	**≥ 2 years**	***P***
N (%)	64 968	37 014 (57.0)	8385 (12.9)	12 696 (19.5)	2850 (4.39)	4023 (6.19)	
Age, years	71.4 ± 11.7	70.7 ± 12.3	72.8 ± 10.2	72.5 ± 10.9	71.6 ± 11.2	72.0 ± 10.8	<0.001
< 70	9286 (14.3)	5881 (15.9)	909 (10.8)	1597 (12.6)	388 (13.6)	511 (12.7)	<0.001
70–79	14 251 (21.9)	8288 (22.4)	1772 (21.1)	2598 (20.5)	659 (23.1)	934 (23.2)	
80–89	24 849 (38.3)	13 958 (37.7)	3371 (40.2)	4931 (38.8)	1046 (36.7)	1543 (38.4)	
≥ 90	16 582 (25.5)	8887 (24.0)	2333 (27.8)	3570 (28.1)	757 (26.6)	1035 (25.7)	
Sex (male)	48 606 (74.8)	27 881 (75.3)	6249 (74.5)	9371 (73.8)	2061 (72.3)	3045 (75.7)	<0.001
Race, *n* (%)							
White	55 169 (84.9)	31 493 (85.1)	7293 (87.0)	10 650 (83.9)	2380 (83.5)	3350 (83.3)	<0.001
Black or mixed black	998 (1.54)	486 (1.31)	74 (0.88)	242 (1.91)	75 (2.63)	120 (2.98)	
Asian or Asian British	2398 (3.69)	1216 (3.29)	226 (2.70)	568 (4.47)	152 (5.33)	237 (5.89)	
Unknown	6403 (9.86)	3819 (10.3)	792 (9.45)	1236 (9.74)	243 (8.53)	316 (7.85)	
Device type, *n* (%)							
CRT-D	32 313 (49.7)	18 781 (50.7)	4021 (48.0)	6090 (48.0)	1457 (51.1)	1966 (48.9)	<0.001
CRT-P	32 655 (50.3)	18 233 (49.3)	4364 (52.1)	6606 (52.0)	1393 (48.9)	2057 (51.1)	
Ischaemic aetiology	44 181 (68.0)	23 819 (64.4)	5726 (68.3)	9249 (72.9)	2173 (76.3)	3214 (79.9)	<0.001
Previous history							
Hypertension	44 917 (69.1)	24 104 (65.1)	5709 (68.1)	9553 (75.2)	2262 (79.4)	3289 (81.8)	<0.001
Diabetes	18 865 (29.0)	9218 (24.9)	2315 (27.6)	4538 (35.7)	1096 (38.5)	1698 (42.2)	<0.001
Chronic kidney disease	11 574 (17.8)	4884 (13.2)	1173 (14.0)	3313 (26.1)	859 (30.1)	1345 (33.4)	<0.001
Myocardial infarction	12 123 (18.7)	6571 (17.8)	1545 (18.4)	2465 (19.4)	630 (22.1)	912 (22.7)	<0.001
Year of implantation							
2010–2011	9169 (14.1)	4708 (12.7)	1181 (14.1)	2068 (16.3)	442 (15.5)	770 (19.1)	<0.001
2012–2013	11 075 (17.1)	6281 (17.0)	1283 (15.3)	2197 (17.3)	490 (17.2)	824 (20.5)	
2014–2015	14 247 (21.9)	8301 (22.4)	1760 (21.0)	2731 (21.5)	590 (20.7)	865 (21.5)	
2016–2017	15 520 (23.9)	8969 (24.2)	2150 (25.6)	2934 (23.1)	647 (22.7)	820 (20.4)	
2018–2019	14 957 (23.0)	8755 (23.7)	2011 (24.0)	2766 (21.8)	681 (23.9)	744 (18.5)	

The table shows the baseline characteristics according to the timing of CRT implantation.
HF, heart failure; HFH, heart failure hospitalization; CRT-D, cardiac resynchronization-defibrillation; CRT-P, cardiac resynchronization-pacing.

Table 2 Clinical outcomes

	Timing of CRT implantation						***P***
	All	**No previous HFH**	**During HFH**	**< 1 year**	**≥ 1 year and < 2 years**	**≥ 2 years**	
Number of CRT implantations	64 968	37 014	8385	12 696	2850	4023	
Total mortality, *n* (%)	26 177 (40.3)	12 931 (34.9)	3129 (37.3)	6233 (49.1)	1472 (51.7)	2411 (59.9)	<0.001
Total HFHs, *n* (%)	15 539 (20.3)	6314 (14.3)	1832 (18.7)	4371 (29.8)	1148 (35.7)	1874 (40.2)	<0.001
First HFHs, *n* (%)	13 814 (21.3)	5797 (15.7)	1633 (19.5)	3835 (30.2)	974 (34.2)	1575 (39.2)	<0.001
Total mortality or first HFHs	30 373 (46.8)	14 797 (40.0)	3717 (44.3)	7326 (57.7)	1742 (61.1)	2791 (69.4)	<0.001

HFH, heart failure hospitalization; CRT, cardiac resynchronization therapy.

Table 3 Univariate analyses

	Total mortality				Total mortality or HFH				HFH			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Age (years)												
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
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
Race												
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
Device type (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
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 of implantation												
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
Timing of CRT implantation*												
During first HFH	1.09	1.05	1.13	<0.001	1.16	1.12	1.20	<0.001	1.29	1.22	1.36	<0.001
< 1 year	1.58	1.54	1.63	<0.001	1.77	1.72	1.82	<0.001	2.31	2.22	2.41	<0.001
≥ 1 year and < 2 years	1.74	1.65	1.83	<0.001	2.01	1.91	2.11	<0.001	2.77	2.59	2.96	<0.001
≥ 2 years	2.03	1.95	2.12	<0.001	2.35	2.26	2.45	<0.001	3.27	3.09	3.45	<0.001
Per year (whole sample)	1.21	1.19	1.22	<0.001	1.25	1.24	1.26	<0.001	1.34	1.32	1.36	<0.001

Results are expressed as hazard ratios and 95% CI.
CRT-D, cardiac resynchronization therapy-defibrillation.
*Refers to the timing of CRT implantation in relation to heart failure hospitalizations (HFH). Comparators are < 60 years for age; white for race. CRT-pacing device for device type; year 2010–2011 for year of implantation; and no previous HFH for timing of CRT implantation.

Total mortality

Over 4.54 (2.80–6.71) years [median (interquartile range); 272 989 person-years], 26 177 (40.3%) patients died (*Table 2*). In univariate analyses (*Table 3*), patients undergoing CRT implantation during the first HFH had a slightly higher total mortality [HR: 1.09; 95% confidence interval (CI): 1.05–1.12] than CRT recipients with no previous HFHs. This risk more than doubled in patients undergoing CRT ≥ 2 years after the first HFH (HR: 2.03 (95% CI 1.95–2.12). Time in years from the first HFH to CRT implantation was associated with a progressively higher total mortality (HR: 1.21; 95% CI 1.19–1.22). Event rates are shown in *Figure 2*. Survival curves are shown in *Figure 3*.

In multivariable analyses, total mortality in patients undergoing CRT at the time of a first HFH was similar to patients with no previous HFHs (HR: 1.01; 95% CI 0.97–1.05) (*Table 4*). Time in years from the first HFH to CRT implantation was associated with a progressively higher risk of total mortality (HR: 1.15; 95% CI 1.14–1.16).

Total mortality or heart failure hospitalizations

A total of 30 373 (46.8%) patients met the composite endpoint of total mortality or HFH after CRT implantation (*Table 2*). In univariate analyses (*Table 3*), patients undergoing CRT implantation during the first HFH had a higher total mortality or HFH [HR: 1.09; 95% confidence interval (CI): 1.05–1.12] than CRT recipients with no previous HFHs. This risk more than doubled in patients undergoing CRT ≥ 2 years after the first HFH (HR: 2.35; 95% CI 2.26–2.45). Time in years from the first HFH to CRT implantation was associated with a progressively higher risk of total mortality or HFH (HR: 1.25; 95% CI 1.24–1.26). Event rates are shown in *Figure 2*. Survival curves are shown in *Figure 3*.

In multivariable analyses (*Table 4*), CRT implantation during a first HFH and thereafter was associated with a higher total mortality or HFH. Time in years from the first HFH to CRT implantation was associated with a progressively higher risk of total mortality or HFH (HR: 1.19; 95% CI 1.17–1.20).

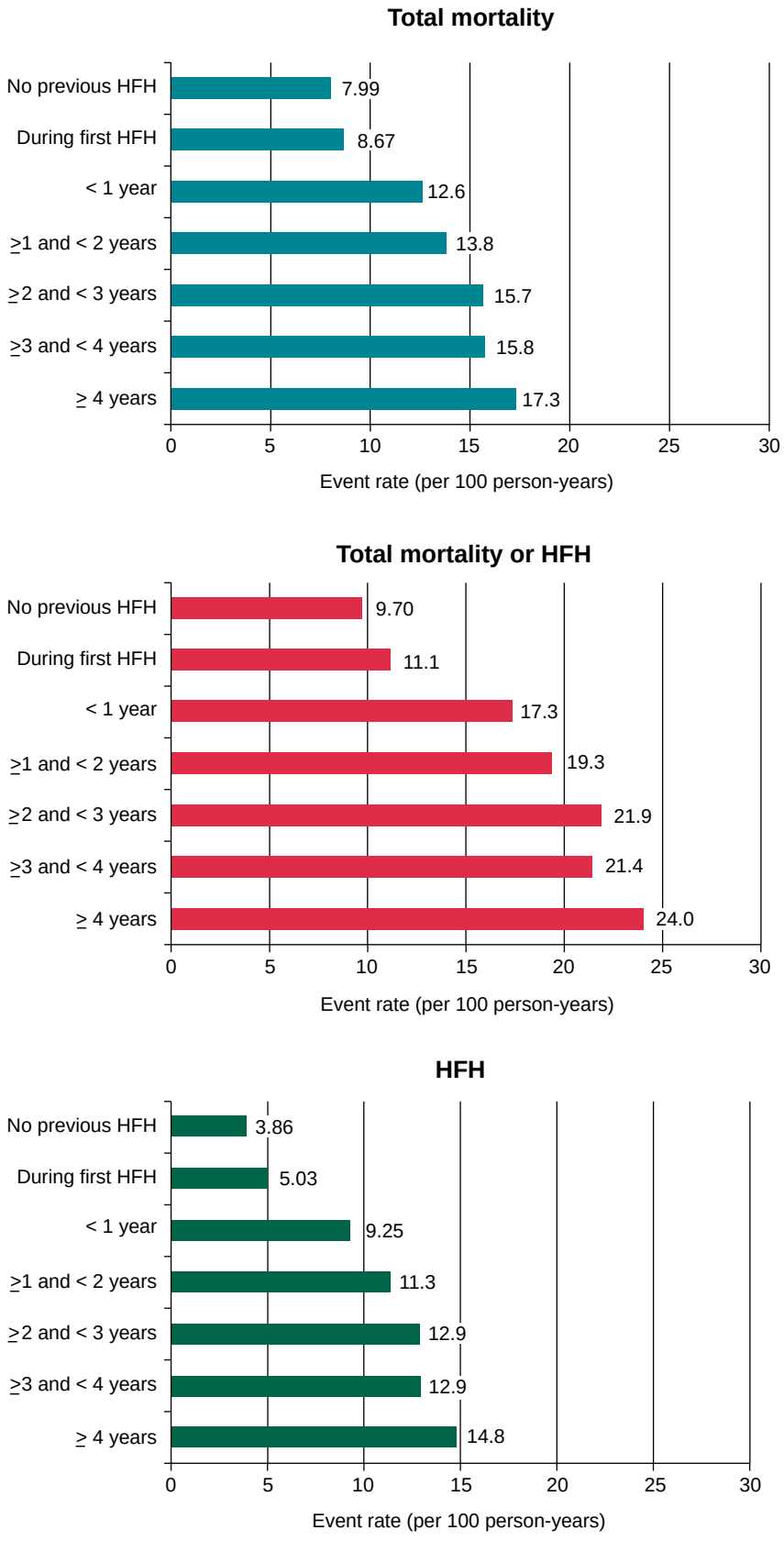
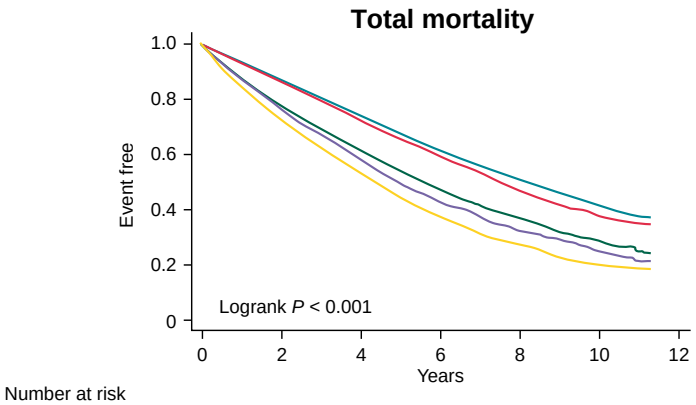
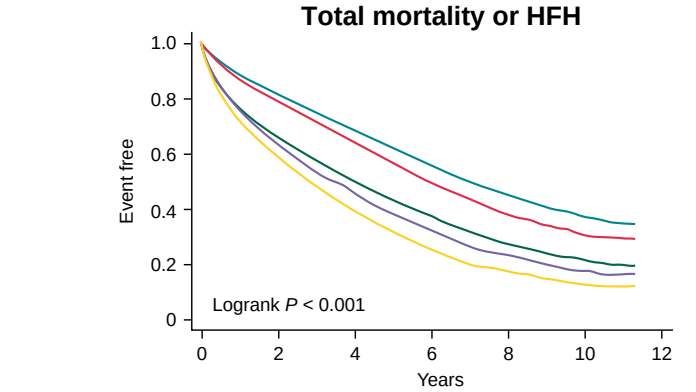


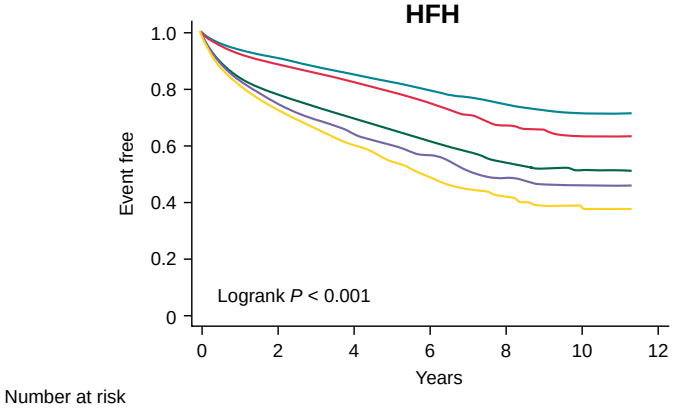
Figure 2 Event rates. Graphs show event rates (number per 100 person-years) for patients undergoing cardiac resynchronization therapy (CRT) in relation to the time from the first heart failure hospitalization (HFH) to CRT implantation.



Number at risk							
No previous HFH	37014	29283	18379	9744	4298	1086	0
During first HFH	8385	6621	4037	2034	923	259	0
HFH to 1 year	12696	9062	5395	2715	1188	341	0
≥1 yr to < 2 yrs	2850	1984	1130	560	235	77	0
≥2 years	4023	2714	1586	798	361	99	0



Number at risk							
No previous HFH	37014	27492	16691	8576	3668	903	0
During first HFH	8385	6081	3546	1693	707	193	0
HFH to 1 year	12696	7704	4370	2063	819	228	0
≥1 yr to < 2 yrs	2850	1625	849	390	140	43	0
≥2 years	4023	2182	1173	517	200	50	0



Number at risk							
No previous HFH	37014	27492	16691	8576	3668	903	0
During first HFH	8385	6081	3546	1693	707	193	0
HFH to 1 year	12696	7704	4370	2063	819	228	0
≥1 yr to < 2 yrs	2850	1625	849	390	140	43	0
≥2 years	4023	2182	1173	517	200	50	0

Figure 3 Kaplan–Meier survival curves for total mortality, heart failure hospitalization (HFH), and the composite endpoint of total mortality of heart failure hospitalization (HFH) according to the timing of cardiac resynchronization therapy (CRT) implantation.

Table 4 Multivariable analyses

	Total mortality				Total mortality or HFH				HFH			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
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
Sex (male)	1.45	1.41	1.49	<0.001	1.35	1.31	1.39	<0.001	1.27	1.22	1.32	<0.001
Race (non-white)	0.97	0.95	0.98	<0.001	0.98	0.97	0.99	0.001	1.01	0.99	1.03	0.203
Device type (CRT-D)	0.91	0.89	0.94	<0.001	0.93	0.91	0.96	<0.001	1.07	1.03	1.11	<0.001
Previous history												
Hypertension	1.10	1.07	1.13	<0.001	1.12	1.09	1.16	<0.001	1.17	1.12	1.22	<0.001
Diabetes	1.30	1.27	1.34	<0.001	1.30	1.26	1.33	<0.001	1.30	1.25	1.35	<0.001
Chronic kidney disease	1.73	1.68	1.78	<0.001	1.68	1.63	1.72	<0.001	1.65	1.58	1.72	<0.001
Myocardial infarction	1.27	1.23	1.31	<0.001	1.29	1.26	1.33	<0.001	1.30	1.25	1.36	<0.001
Year of implantation												
2012–2013	0.91	0.88	0.95	<0.001	0.89	0.86	0.93	<0.001	0.85	0.81	0.90	<0.001
2014–2015	0.84	0.81	0.87	<0.001	0.79	0.76	0.82	<0.001	0.70	0.66	0.73	<0.001
2016–2017	0.79	0.76	0.82	<0.001	0.73	0.71	0.76	<0.001	0.62	0.59	0.66	<0.001
2018–2019	0.76	0.72	0.80	<0.001	0.63	0.61	0.66	<0.001	0.44	0.41	0.47	<0.001
Timing of CRT implantation*												
At first HFH	1.01	0.97	1.05	0.643	1.09	1.05	1.13	<0.001	1.25	1.18	1.32	<0.001
At < 1 year	1.35	1.31	1.39	<0.001	1.53	1.49	1.58	<0.001	2.05	1.96	2.13	<0.001
At ≥1 year and < 2 years	1.50	1.42	1.58	<0.001	1.74	1.65	1.83	<0.001	2.39	2.23	2.56	<0.001
At ≥ 2 years	1.67	1.60	1.75	<0.001	1.92	1.84	2.00	<0.001	2.63	2.48	2.78	<0.001
Per year (whole sample)	1.15	1.14	1.16	<0.001	1.19	1.17	1.20	<0.001	1.26	1.24	1.28	<0.001

Results are expressed as hazard ratios and 95% CI. In the multivariable analysis of each variable, independent covariables comprised all other variables listed above. For example, in the analysis of age, independent covariables included sex; race; device type; previous history of hypertension, diabetes, chronic kidney disease, and/or myocardial infarction; and year of implantation and time (in years) from the first heart failure hospitalization (HFH). Comparators were < 60 years for age; white for race; CRT-pacing device for device type; year 2010–2011 for year of implantation; and no previous HFH for timing of CRT implantation.
CRT-D, cardiac resynchronization therapy-defibrillation.

Heart failure hospitalizations

A total of 15 539 HFHs occurred any time after CRT implantation, of which 13 814 (21.3%) were first HFHs. In univariate analyses (*Table 3*), patients undergoing CRT implantation during the first HFH had a higher HFH (HR: 1.29; 95% CI: 1.22–1.36]) after CRT than that of CRT recipients with no previous HFHs. This risk more than trebled in patients undergoing CRT ≥ 2 years after the first HFH (HR: 3.27; 95% CI 3.09–3.45). Time in years from the first HFH to CRT implantation was associated with a higher risk of HFH (HR: 1.34; 95% CI 1.32–1.36). Similar trends were observed in multivariable analyses (*Table 4*).

Discussion

This is the first study to explore the timing of CRT device implantation in relation to HFHs from the perspective of a public healthcare system covering an entire nation. Several main findings have emerged (Graphical Abstract). First, the best outcomes were observed in patients with no previous HFH. Second, CRT implantation during a first HFH was associated with comparable outcomes. Third, progressively worse outcomes were observed for increasing time from a first HFH to CRT implantation. Last, these trends were evident after correction for age, sex, race, device type (CRT-D or CRT-*P*), HF aetiology, and comorbidities, including chronic kidney disease, diabetes mellitus, and hypertension. These findings suggest that clinical outcomes after CRT are most favourable in patients who undergo implantation in the absence of a previous HFH and in patients undergoing implantation during their first HFH.

A HFH marks a defining point in the trajectory of HF. In the 2009 to 2010 European Society of Cardiology–Heart Failure HF pilot survey, patients with acute HF had a total mortality rate of 17.4% and a re-hospitalization rate of 43.9% at 1 year[8] In the US Medicare and Medicaid Get With The Guidelines–Heart Failure dataset (39 982 patients from 254 hospitals), the 5-year survival after a HFH was 24.6% and the median survival was 2.1 years.[9] Arguably, such high risks might be expected to compromise the long-term benefits of CRT.

The landmark CRT trials of CRT excluded patients undergoing CRT implantation during a HFH,[1] and therefore, clinical guidelines do not recommend CRT implantation in these patients. However, we, as others,[4,6,7] have found that CRT implantation is being undertaken as a non-elective procedure in routine clinical practice. For hospitalized patients, important questions for clinicians are as follows: should one undertake CRT implantation during a first HFH? And, if a HFH has occurred, when should CRT implantation be undertaken? In this regard, patients undergoing CRT during a first HFH had a similar risk of total mortality. The risks of total mortality/HFH or HFH *per se* were higher, but only marginally. Much worse outcomes were observed in patients undergoing CRT after a first HFH. Each year from a first HFH to CRT implantation was associated with a 21% higher risk of total mortality and a 34% higher risk of HFH, compared to patients with no previous HFH prior to CRT.

Our findings have emerged in the context that clinical guidelines recommend that CRT implantation should be delayed for 3 months after the diagnosis of HF, to allow for the reverse LV remodelling effects of medical therapy. In practice, however, this delay is considerably longer.[2] In the US National Cardiovascular Data Registry, over two-thirds of CRT implantations were implanted >9 months after the initial diagnosis of HF.[10] We found that the median delay from a first HFH to CRT implantation was 6.9 months, with 42.8% of patients undergoing CRT implantation after ≥ 9 months.

The delay to the delivery of any therapy in HF plays on the balance between three trajectories: complete recovery, remission, and/or inexorable progression.[11] In the field of CRT, complete recovery or remission is most likely in the context of a left bundle branch block (LBBB)–induced cardiomyopathy in the absence of an irreversible cardiomyopathy, whereas inexorable progression is most likely in an irreversible cardiomyopathy with a bystander LBBB.[12] In this mix, we should consider that continued exposure to a LBBB leads to detrimental effects on myocardial metabolism, structure, and function.[13,14] These findings are consistent with the observation that an incidental LBBB carries a significant risk of cardiovascular events.[15] The importance of early correction of a LBBB was suggested by the NEOLITH (NEw-Onset LBBB-Associated Idiopathic Nonischemic CardiomyopaTHy) II study, in which a shorter time from diagnosis to CRT was associated with superior left ventricular reverse remodelling in patients with a LBBB.[16]

We should also consider that no HF drugs have been shown to correct conduction abnormalities. Moreover, it is doubtful whether they are effective in their presence. This was suggested by NEOLITH, in which improvements in LVEF after 3 months of medical therapy in patients with a LBBB were marginal.[17] Sze et al. also showed that in patients with a baseline LVEF <35% and LBBB, LVEF after 3 to 6 months of medical therapy improved by 2.03% among patients with LBBB, compared with 8% among patients with a normal QRS duration.[5] Huang et al. recently found that treatment with sacubitril/valsartan for 1 year had marginal effects on LVEF in CRT-eligible patients with either a LBBB or with a QRS duration ≥ 150 ms and a non-LBBB intraventricular conduction defect.[18]

Limitations

The typical limitations of retrospective, observational studies based on administrative datasets are acknowledged. Unfortunately, left ventricular function, ECG variables, or medications, all of which are known to impact on clinical outcomes, were not available. It is possible that patients receiving CRT after the first HFH may not have met LVEF and QRS duration criteria for implantation at the time of the first HFH. However, temporal changes in QRS duration (increase by 5–6 ms over 1 year[19]) and LVEF (increase by 2.7% over 1 year[20]) in HF patients are modest. It is also possible that patients receiving CRT at the first HFH were more optimally treated with HF medications than patients implanted after discharge, although the opposite seems more likely. Whilst we have adjusted for comorbidities and other observed variables, this is not synonymous with randomization. Unfortunately, our national database does not allow tracking of patients from primary care or within secondary care. We are therefore unable to comment on the referral pathway leading to CRT implantation.

Conclusions

In this study of a healthcare system covering an entire nation, the timing of CRT implantation was associated with profound differences in long-term clinical outcomes. The best outcomes after CRT implantation were observed in patients with no previous HFHs and in those undergoing implantation during the first HFH. Increasing time from a first HFH to CRT implantation was associated with progressively worse outcomes. These findings suggest that in CRT-eligible patients, implantation should be undertaken before or during the first HFH.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

A.Z.: unrestricted educational grant from Medtronic; T.Q.: unrestricted educational grant from Boston Scientific. FL 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.

Conflicts of interests: None declared.

Data availability

The summary data are available from the corresponding author on request.

References

1. 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.
2. Mullens W, Auricchio A, Martens P, Witte K, Cowie MR, Delgado V *et al.* Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care. *Europace* 2021;**23**:1324–42.
3. Steffel J, Milosevic G, Hürlimann A, Krasniqi N, Namdar M, Ruschitzka F *et al.* Characteristics and long-term outcome of echocardiographic super-responders to cardiac resynchronisation therapy: 'real world' experience from a single tertiary care centre. *Heart* 2011;**97**:1668–74.
4. Goldstein SA, Mentz RJ, Hellkamp AS, Randolph TC, Fonarow GC, Hernandez A *et al.* Timing of cardiac resynchronization therapy device implantation in heart failure patients and its association with outcomes. *Clin Cardiol* 2019;**42**:256–63.
5. Sze E, Samad Z, Dunning A, Campbell KB, Loring Z, Atwater BD *et al.* Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block. *J Am Coll Cardiol* 2018;**71**:306–17.
6. Normand C, Linde C, Blomström-Lundqvist C, Stellbrink C, Gasparini M, Anker SD *et al.* Adherence to ESC cardiac resynchronization therapy guidelines: findings from the ESC CRT survey II. *Europace* 2020;**22**:932–8.
7. Sandhu A, Bao H, Minges KE, Varosy PD, Borne RT, Zipse MM *et al.* Use of cardiac resynchronization therapy defibrillator in US hospitals. *JAMA Cardiol* 2019;**4**: 804–9.
8. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozdz J *et al.* EURObservational research programme: regional differences and 1-year follow-up results of the heart failure pilot survey (ESC-HF pilot). *Eur J Heart Fail* 2013;**15**: 808–17.
9. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF *et al.* Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol* 2017;**70**:2476–86.
10. Zusterzeel R, Spatz ES, Curtis JP, Sanders WE, Selzman KA, Piña IL *et al.* Cardiac resynchronization therapy in women versus men: observational comparative effectiveness study from the national cardiovascular data registry. *Circ Cardiovasc Qual Outcomes* 2015;**8**:S4–11.
11. Wilcox JE, Fonarow GC, Ardehali H, Bonow RO, Butler J, Sauer AJ *et al.* "Targeting the heart" in heart failure: myocardial recovery in heart failure with reduced ejection fraction. *JACC Heart Fail* 2015;**3**:661–9.
12. Wang NC, Adelstein EC, Singh M, Voigt AH, Saba S. Left bundle branch block-associated cardiomyopathies and early cardiac resynchronization therapy: conceptualizing a tailored approach. *J Am Coll Cardiol* 2018;**71**:1943–4.
13. Surkova E, Badano LP, Bellu R, Aruta P, Sambugaro F, Romeo G *et al.* Left bundle branch block: from cardiac mechanics to clinical and diagnostic challenges. *Europace* 2017;**19**: 1251–71.
14. Dupuis LJ, Arts T, Prinzen FW, Delhaas T, Lumens J. Linking cross-bridge cycling kinetics to response to cardiac resynchronization therapy: a multiscale modelling study. *Europace* 2018;**20**:iii87–93.
15. Zegard A, Okafor O, de Bono J, Steeds R, Hudsmith L, Stegemann B *et al.* Prognosis of incidental left bundle branch block. *Europace* 2020;**22**:956–63.
16. Wang NC, Li JZ, Adelstein EC, Althouse AD, Sharbaugh MS, Jain SK *et al.* New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and time from diagnosis to cardiac resynchronization therapy: the NEOLITH II study. *Pacing Clin Electrophysiol* 2018;**41**:143–54.

17. Wang NC, Singh M, Adelstein EC, Jain SK, Mendenhall GS, Shalaby AA *et al.* New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and left ventricular ejection fraction response to guideline-directed therapies: the NEOLITH study. *Heart Rhythm* 2016;**13**:933–42.
18. Huang HT, Huang JL, Lin PL, Lee YH, Hsu CY, Chung FP *et al.* Clinical impacts of sacubitril/valsartan on patients eligible for cardiac resynchronization therapy. *ESC Heart Fail* 2022;**9**:3825–3835.
19. Shamim W, Yousufuddin M, Cicoria M, Gibson DG, Coats AJ, Henein MY. Incremental changes in QRS duration in serial ECGs over time identify high risk elderly patients with heart failure. *Heart* 2002;**88**:47–51.
20. Breathett K, Allen LA, Udelson J, Davis G, Bristow M. Changes in left ventricular ejection fraction predict survival and hospitalization in heart failure with reduced ejection fraction. *Circ Heart Fail* 2016;**9**:e002962.