

Improved prognosis after cardiac resynchronization therapy over a decade

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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

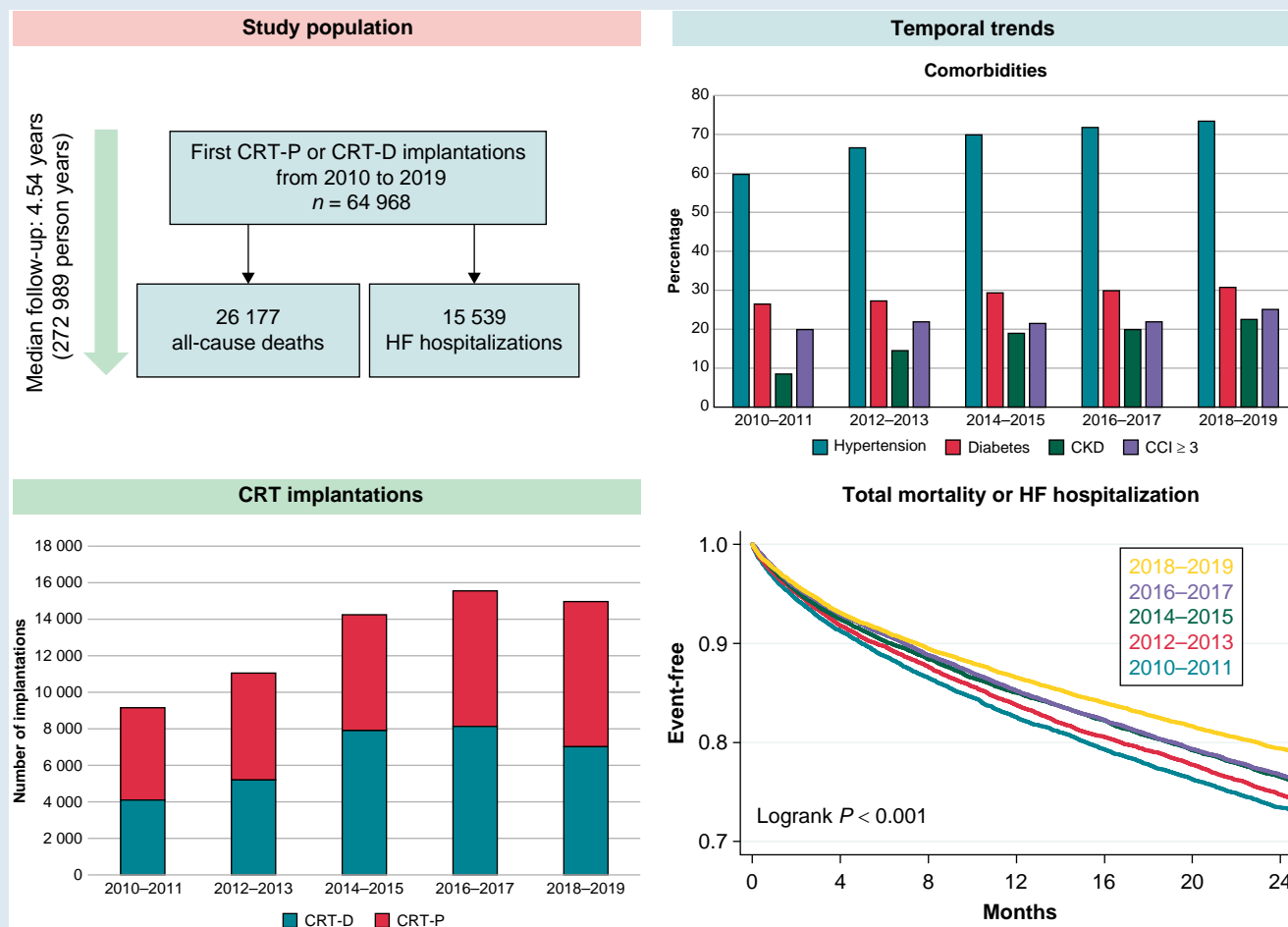
From the perspective of an entire public health system, survival has improved and HF hospitalizations have decreased after CRT implantation over the past decade. This prognostic improvement has occurred despite an increasing comorbidity burden.

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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 index⁹ (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 (\pm 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

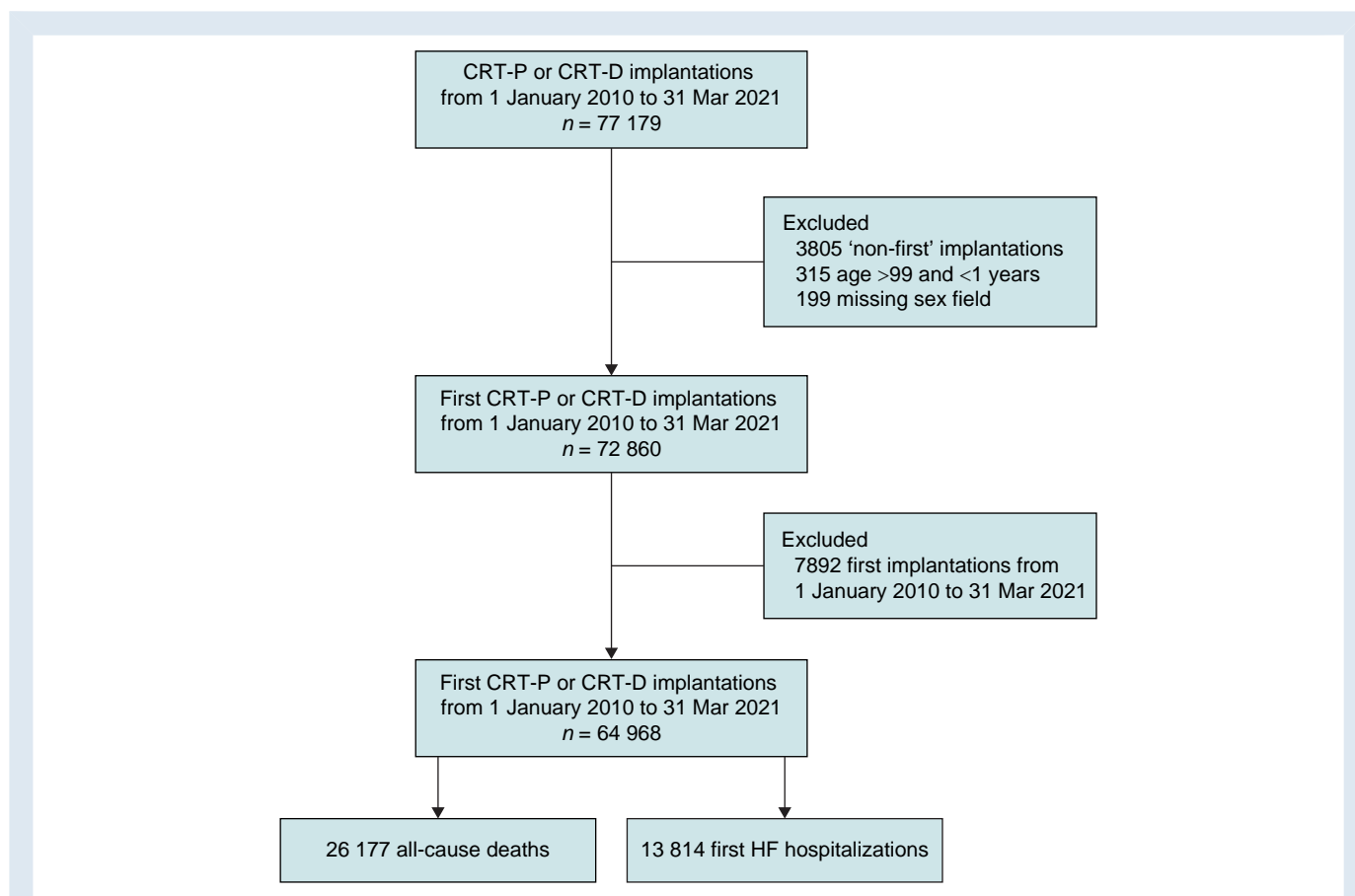


Figure 1 Derivation of the study cohort. CRT-P, cardiac resynchronization therapy-pacemaker; CRTD, cardiac resynchronization therapy-defibrillator.

$P \leq 0.05$ 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 \pm 11.7 | 70.2 \pm 11.8 | 70.9 \pm 11.6 | 71.5 \pm 11.6 | 71.8 \pm 11.6 | 72.1 \pm 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 |

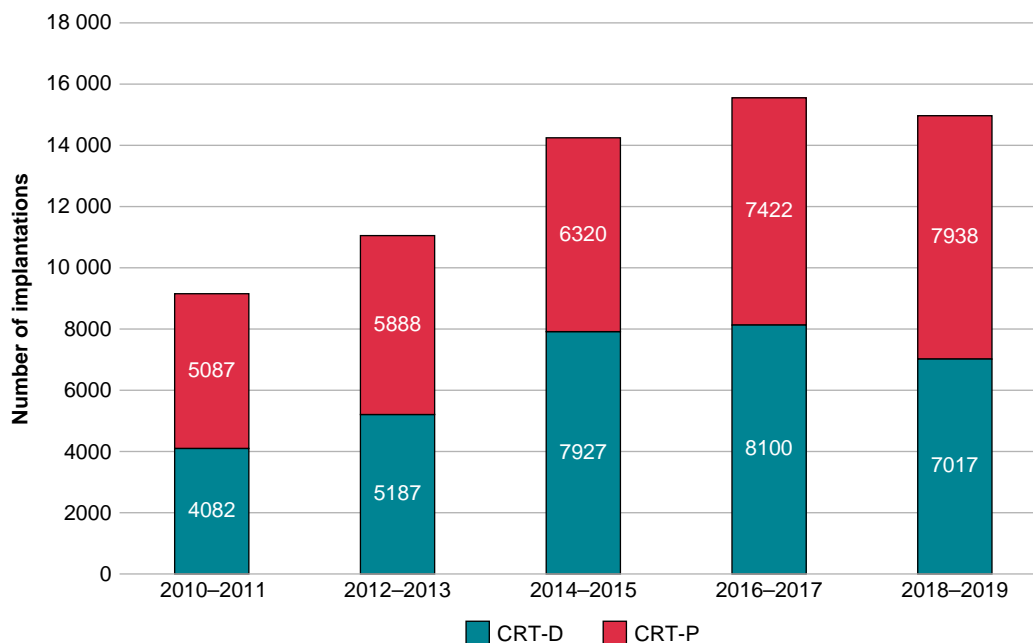


Figure 2 Temporal trends in CRT-P and CRT-D implantation. Absolute number of implantations in England from 2010 to 2019 are shown, grouped into 2 year periods. A significant increase was observed over the decade ($P < 0.001$). CRT-P, cardiac resynchronization therapy-pacemaker; CRTD, cardiac resynchronization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

^aCompared with white race.^bComparison 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.

^aComparison 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

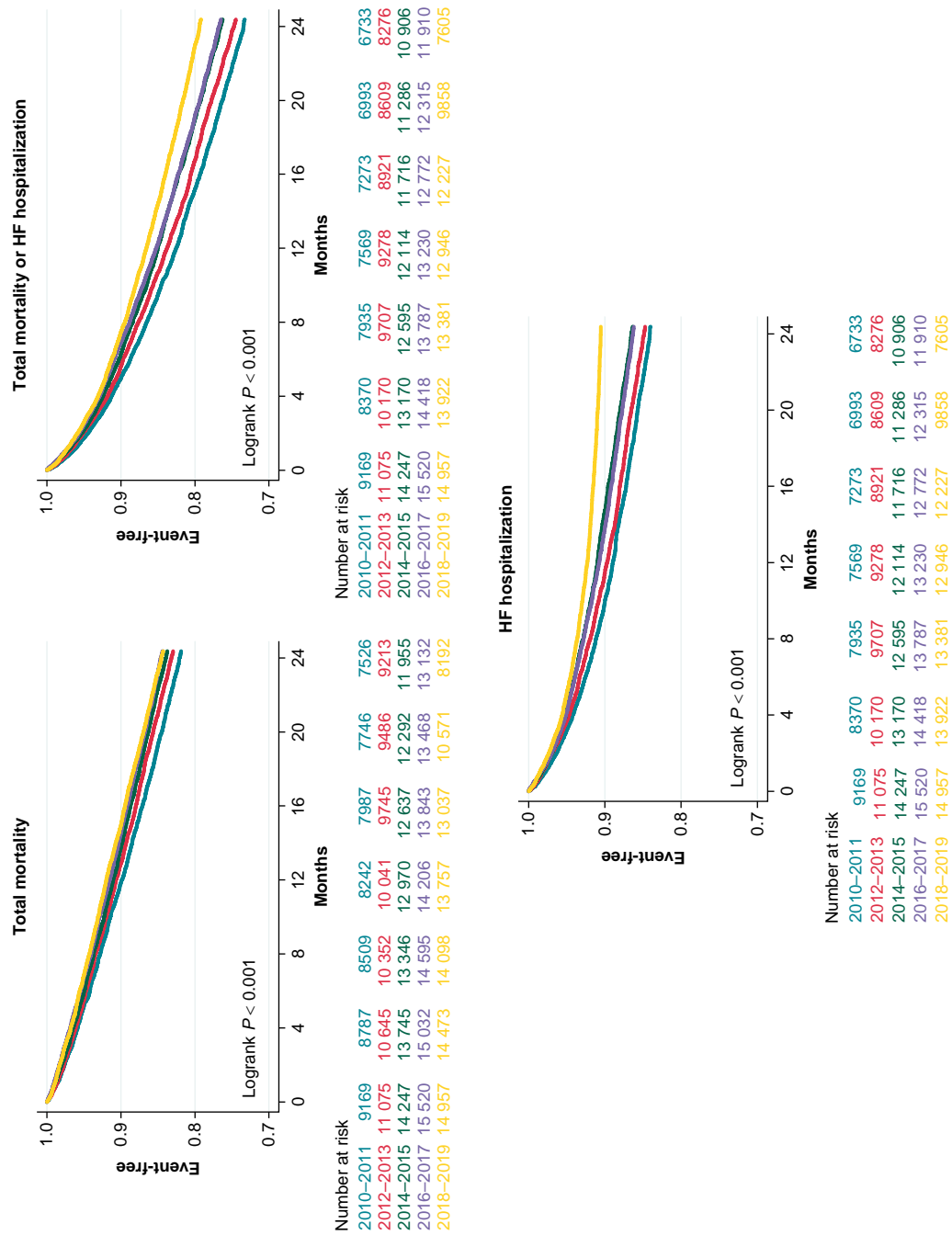


Figure 3 Survival curves: temporal trends. Graphs show Kaplan–Meier survival curves for the three endpoints, according to 2 year cohorts.

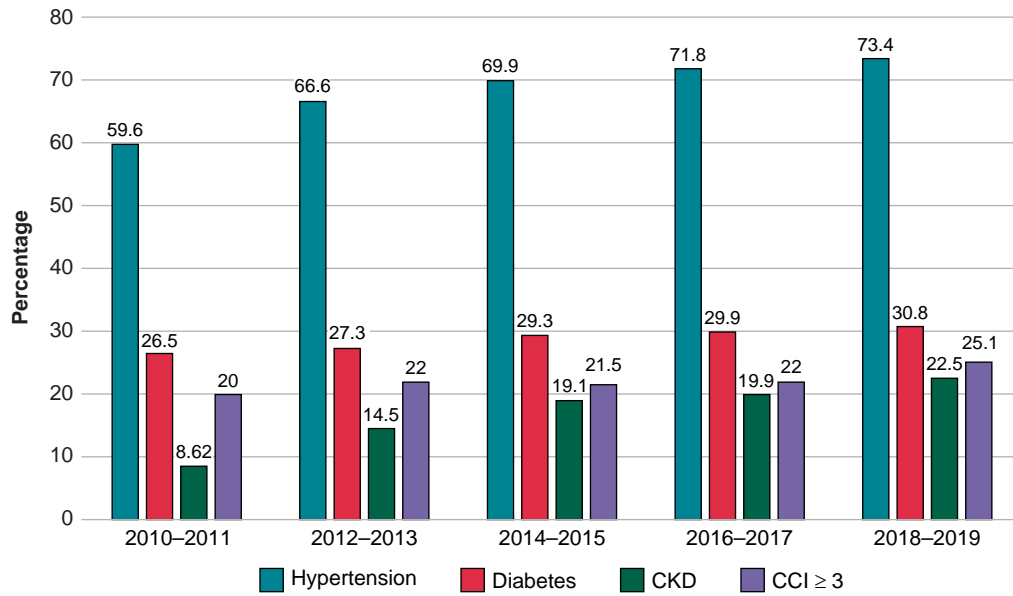


Figure 4 Progression of comorbidities over time. The histograms show the proportion of patients with hypertension, diabetes mellitus, and chronic kidney disease (CKD) over the study period. CCI, Charlson comorbidity index.

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 CRT¹⁴ over the years may have contributed. The formalization of the care of patients with HF¹⁵ 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

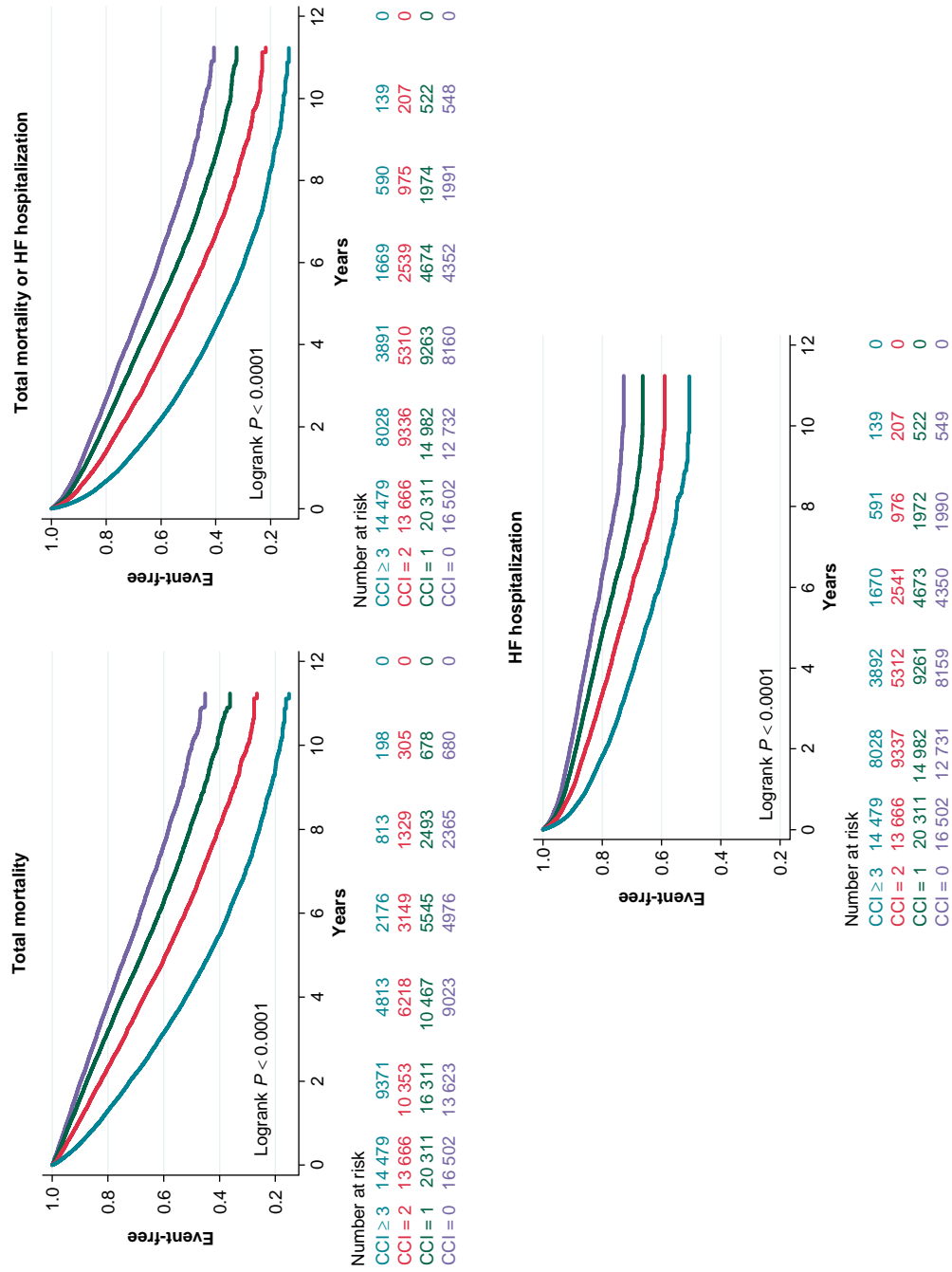


Figure 5 Survival curves: effect of comorbidities. Graphs show Kaplan–Meier survival curves for the three endpoints in the entire cohort, grouped according to the Charlson comorbidity index (CCI). CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator.

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.

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