ORIGINAL RESEARCH ARTICLE

Five-year survival and use of hospital services following ICD and CRT implantation: comparing real-world data with RCTs

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Abstract

Aims   Guidelines recommend the use of an implantable cardioverter-defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) device based on the results of randomized controlled trials (RCTs), typically with selected patients and short follow-up.

Methods and results   We describe the 5 year survival rate and use of hospital services following ICD and CRT implantation in England from April 2011 to March 2013 using the national hospital administrative database covering emergency department visits, inpatient admissions, and clinic appointments, linked to the national death register. Five-year survival was 64% after ICD implantation and 58% after CRT implantation, with median survival times of 6.8 and 6.2 years, respectively. Hospital use was high in both device groups, for the 5 years prior and after implantation, peaking around the implantation date. Most hospital activity was not primarily related to heart failure. Healthcare costs were dominated by admissions, but emergency department and clinic activity were both high. Only the CRT group saw total per-patient costs fall after the index month (implantation), driven by a slight fall in the heart failure admission rate. Patients were typically older than in the trials, but with similar co-morbidity except for substantially more atrial fibrillation and less dementia. Survival and device complications were similar to the RCTs.

Conclusions   Clinical and cost-effectiveness assessments of ICD and CRT implantation are supported by real-world data, although the prevalence of atrial fibrillation remains substantially higher than in the RCTs.

Introduction

Heart failure (HF) is a growing public health problem. The UK prevalence of HF increased by 23% from 2002 to 2014, a trend set to continue despite care improvements, due to population growth and ageing.[1] Co-morbidity among those with HF is increasing steeply: the median number of co-morbidities increased from 3 to 5 in the UK from 2002 to 2014.[1] Estimates suggest that only half of those diagnosed survive 5 years.[2,3]

Heart failure is an expensive condition to manage and places considerable strain on healthcare systems. HF is the most common reason for hospital admissions among those over 65, and, as in many high-income countries, its cost accounts for 2% of the UK National Health Service (NHS) annual expenditure.[4]

Implanting a cardiac device such as an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) is indicated for certain HF patients,[5–7] based on the results of randomized controlled trials (RCTs). In

England, there has been a steady increase in the number of implantations[8,9] since an appraisal in 2014 by the National Institute for Health and Care Excellence (NICE),[6] based on extrapolations from the RCTs, which typically enrol a highly selected patient population and report relatively short follow-up periods, rarely beyond 30 months.[10–17]

With real-world national administrative data, we explored the 5 year survival rate and use of hospital services following ICD and CRT implantation in one large healthcare system (England) and compare this with relevant RCT results.

Methods

Data

We extracted records from England's national hospital administrative database, Hospital Episode Statistics (HES), which comprises over 125 million admitted patient, outpatient, and emergency department (ED) records from the NHS annually. Each admission is assigned a primary ICD-10 diagnostic code by trained staff who determine this to be the primary reason for treatment; 19 secondary ICD-10 codes capture co-morbidities or complications during the admission. Up to 24 procedures are coded using the UK's OPCS system (Office of Population Censuses and Surveys). ED records use a much broader and more symptom-based approach. HES database is linked to the national deaths registry, thereby capturing the date and causes of all deaths, including out-of-hospital deaths. HES has complete coverage across all NHS hospitals in England. We used HES data from April 2006 to March 2018 to track back 5 years to exclude patients with prior implants. Linked death register data were available to July 2018; reliable ED records only existed from April 2009.

Cohorts and outcomes

We defined three cohorts in April 2011 to March 2013: CRT, ICD, and first hospitalization for HF with no-device implantation. In the device groups, we identified the inpatient admission record covering the implantation of each patient's first such device during the 2 years: this was their 'index date'. Patients with records with codes for the implantation or removal of such devices in the previous 5 years were excluded.

For the no-device group, the date of first discharge for an admission for HF (ICD-10 I50) during the 2 years was taken as their index date: the patient characteristics and crude death rate for this group are given for context only. Patients with records with HF recorded in any admission diagnosis field in the previous 5 years were excluded. Co-morbidities were derived from the index admission and any admission in the previous year for all groups.

Total mortality, hospital activity by sector—clinic, ED, day case, and inpatient admission—and associated NHS reference costs were the main outcomes. Admissions were divided into that for HF and that for any 'non-HF' conditions using the primary diagnosis field. For device patients, we identified post-implantation admissions for removal, resiting, or renewal (replacement) of the device. The Supporting Information, *Appendix* gives the procedure codes.

Analysis

A Kaplan–Meier plot described the 5 year mortality and median survival since the index date for each group, and log-rank tests compared the curves; due to long survival times, for ICD implants, this could not estimate the median, so a linear survival model was fitted and the mean survival time estimated. For hospital activity and reference costs, we calculated the monthly rates per patient at risk, that is, per patient still alive, for 5 years before, and after, the index month, giving 121 months (periods of 30 days) in total. Poisson regression was used to test for changes in hospital use after the index month.

Results

For the two index years, 265 519 patients had a first admission for HF but with no device, 5512 patients had a first CRT implantation recorded, and 3528 patients had a first ICD implant recorded. Very few had a secondary procedure code to allow us to distinguish reliably between CRT-P (pacing only) and CRT-D (CRT with defibrillator function), so we labelled both groups as the CRT group.

Patient characteristics

The mean age for CRT patients was 73 and for ICD was 68; two-thirds of CRT patients were male, as were 83% of ICD patients. Device patients were on average younger and much more likely to be male than typical HF admissions; co-morbidities were very common and similar in all groups except for there being few people with coded dementia in the device groups (*Table 1*).

Overall survival

Five years after the index date, all-cause death rates were 67.6% for those with no device, 41.8% for the CRT group, and 35.9% for the ICD group. Median survival was 2282 days (6.2 years) for CRT; mean survival for ICD patients was

Table 1 Patient characteristics

Factor	CRT	ICD	No device
All patients	5512	3528	265 519
Mean age (SD)	73.2 (11.1)	67.7 (11.5)	78.0 (12.4)
Age 18–39	64 (1.2%)	77 (2.2%)	2584 (1.0%)
Age 40–64	965 (17.5%)	1092 (31.0%)	33 675 (12.7%)
Age 65–74	1498 (27.2%)	1262 (35.8%)	47 320 (17.8%)
Age 75–84	2333 (42.3%)	996 (28.2%)	90 853 (34.2%)
Age 85+	652 (11.8%)	101 (2.9%)	91 087 (34.3%)
Female	1752 (31.8%)	591 (16.8%)	134 472 (50.6%)
Male	3760 (68.2%)	2937 (83.2%)	131 047 (49.4%)
Diabetes	1442 (26.2%)	985 (27.9%)	63 608 (24.0%)
Living alone	183 (3.3%)	97 (2.7%)	12 729 (4.8%)
CABG	69 (1.3%)	103 (2.9%)	2452 (0.9%)
PCI	227 (4.1%)	379 (10.7%)	8792 (3.3%)
Median (IQR) number of co-morbidities as listed below	3 (2–4)	3 (2–4)	3 (2–4)
Number of co-morbidities as listed below: 0	268 (4.9%)	112 (3.2%)	10 120 (3.8%)
1	795 (14.4%)	401 (11.4%)	37 147 (14.0%)
2	1177 (21.4%)	680 (19.3%)	63 357 (23.9%)
3	1209 (21.9%)	832 (23.6%)	66 197 (24.9%)
4	951 (17.3%)	743 (21.1%)	48 127 (18.1%)
5+	1112 (20.2%)	760 (21.5%)	40 575 (15.3%)
Previous stroke	84 (1.5%)	71 (2.0%)	10 212 (3.8%)
Previous pneumonia	358 (6.5%)	348 (9.9%)	55 327 (20.8%)
Ischaemic heart disease	3215 (58.3%)	2789 (79.1%)	116 926 (44.0%)
Atrial fibrillation	2669 (48.4%)	1484 (42.1%)	111 097 (41.8%)
Valvular disorders	1869 (33.9%)	1105 (31.3%)	52 115 (19.6%)
Hypertension	3151 (57.2%)	2014 (57.1%)	154 556 (58.2%)
Peripheral vascular disease	602 (10.9%)	425 (12.0%)	19 418 (7.3%)
Chronic pulmonary disease	1252 (22.7%)	699 (19.8%)	63 871 (24.1%)
Renal disease	1131 (20.5%)	582 (16.5%)	49 205 (18.5%)
Obesity	320 (5.8%)	251 (7.1%)	12 461 (4.7%)
Dementia	41 (0.7%)	18 (0.5%)	19 682 (7.4%)
Depression	167 (3.0%)	112 (3.2%)	11 824 (4.5%)
Other mental health condition	582 (10.6%)	626 (17.7%)	38 298 (14.4%)

CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PCI, percutaneous coronary intervention; SD, standard deviation.
All continuous variables with normal distribution show as means ± standard deviation. Number of co-morbidities is shown as median (25th–75th percentile).

2478 days (6.8 years). Log-rank tests revealed highly significant differences between ICD and CRT ($P < 0.001$; *Figure 1*).

For both groups, HF was given as the main cause for fewer than one in three deaths: 27.5% of the 2305 deaths for CRT and 31.0% of the 1265 deaths for ICD, with 22.7% and 23.8% being for other cardiovascular causes for CRT and ICD, respectively.

Hospital activity comparisons between groups

Figure 2 shows hospital admissions for the ICD patients, expressed as admissions per patient at risk; the peak is at 1, but we have shortened the *Y*-axis for clarity. This pattern of the unplanned (length of stay > 0 days) admissions dominating for the index admission and being the commonest type of admission both before, and after, the index date is repeated for the other groups, although for CRT, the majority of the index admissions (for implantation) were elective. In *Figure 3*, all admissions (elective inpatient admissions, day cases, and emergency inpatient admissions) have been split by the coded primary diagnosis into two groups: HF and non-HF

admissions. *Figure 3* is for ICD only, but the patterns are similar for the other group (not shown). *Figure 4* compares the ICD and CRT groups for all admissions.

The ED visit rates for both groups rose only slightly after implantation (Supporting Information). Outpatient department (OPD) appointment rates rose to a peak in the index month and remained high for both groups (Supporting Information).

Hospital activity and costs before, and after, the index month

Table 2 and Poisson regression show that total admission rates (inpatient and day case) per patient at risk fell after the index month for the CRT and ICD groups, although the latter fall was small. Consequently, for hospital admissions, the CRT group was the only group that showed a fall in the mean cost per patient at risk after the index month (from £328 to £288 per month, compared with little change—£262 to £270—for the ICD group; Supporting Information).

Figure 1 Kaplan–Meier survival plot for the two device groups and those with no device. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.
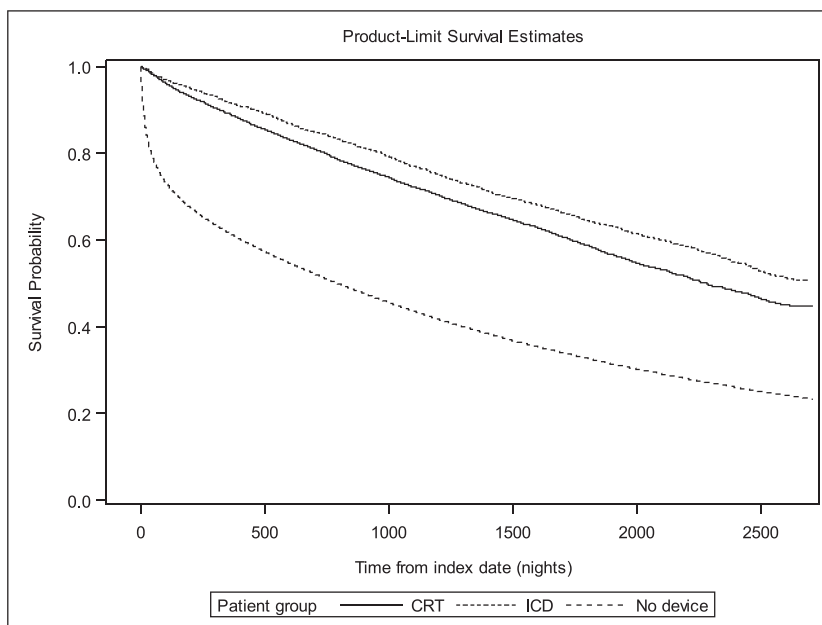

Figure 2 Admissions for the implantable cardioverter-defibrillator patients (NB: peak is at 1; *Y*-axis shortened for clarity). LOS, length of stay.
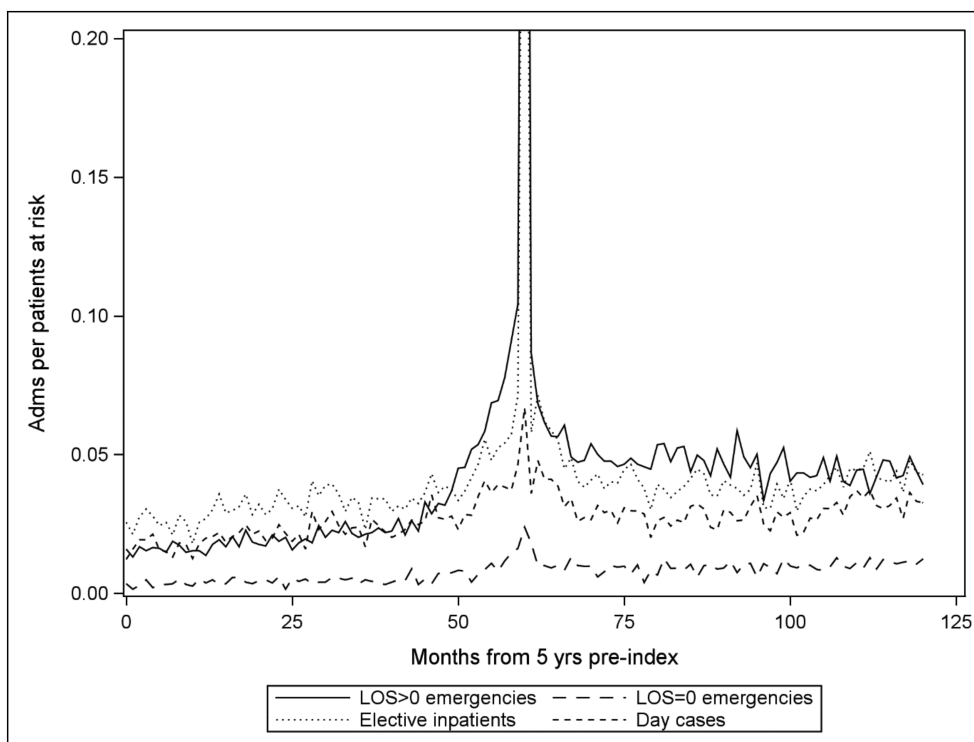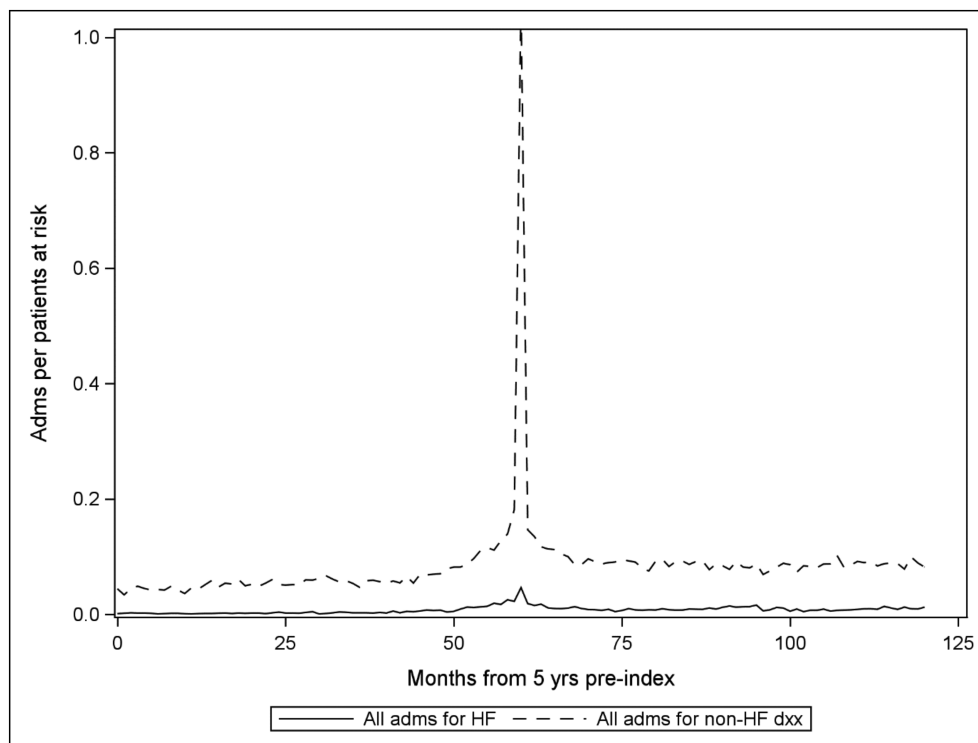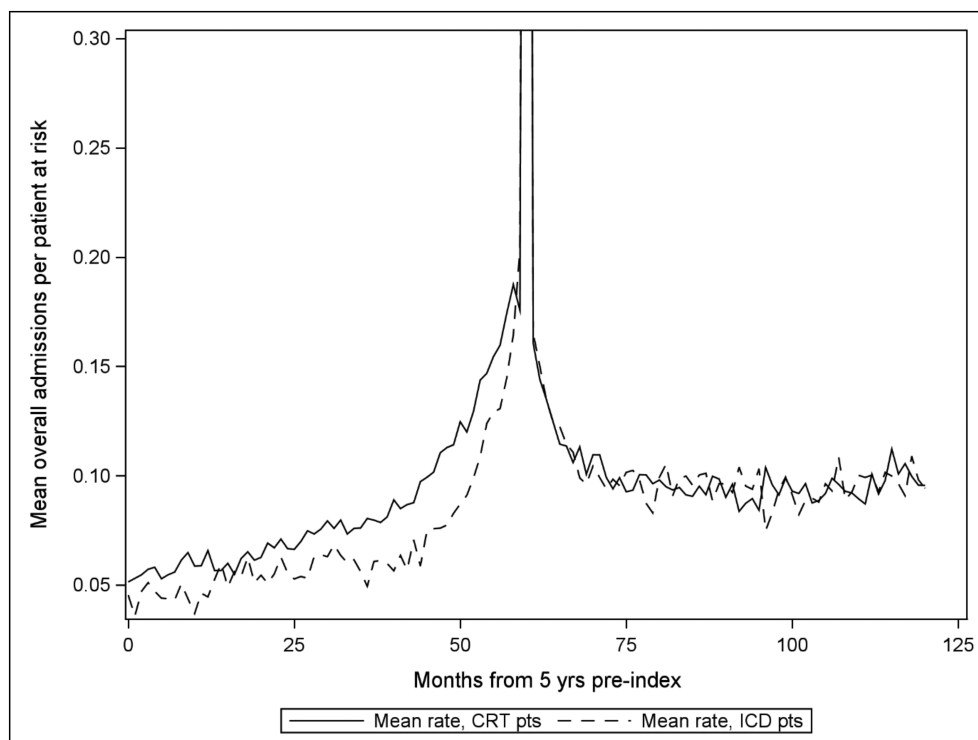
Figure 3 Admissions for the implantable cardioverter-defibrillator group split by the primary diagnosis into heart failure (HF) vs. non-HF.

Figure 4 Total admission rate by patient group (*Y*-axis peaks at 1). CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

Table 2 Total inpatient and day case admissions by primary diagnosis for each group in the 12 months before and the 12 months after the index month (index month not included)

Patient group	Type of admission	Total admissions		Mean admissions per patient at risk	
		12 months before index	12 months after index	12 months before index	12 months after index
CRT	All	9605	7402	0.145	0.120
	HF	1330	622	0.020	0.010
	Non-HF	8275	6780	0.125	0.110
ICD	All	5086	4766	0.120	0.118
	HF	565	471	0.013	0.012
	Non-HF	4521	4295	0.107	0.107

CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator.

For both groups, the peak in ED visits occurred during the index month (Supporting Information). Mean OPD appointment costs per patient at risk rose in all groups after the index month (Supporting Information).

The estimated total NHS reference costs for *all* hospital activity (ED, admission, and OPD reviews) per patient at risk in the 12 months before, and the 12 months after, the index month were £4960 and £4713 for CRT and £3972 and £4633 for ICD. This shows that only CRT saw total per-patient NHS costs fall after the index month.

Admissions for device complications

Excluding replacements, complication rates for ICD were approximately double that for CRT. The ICD group had rates of 9.8% for mechanical complication, infection, and inflammatory reaction and resiting of device and 2.8% for other and unspecified complications. These rates for CRT were 5.8% and 1.6%, respectively.

In the minority of patients whose device was replaced during the 5 year study period [425 (10.8%) for ICD and 289 (5.0%) for CRT], the median time to replacement for ICD was 1311 days (3.6 years), and 829 days (2.2 years) for CRT, with mean of 1008 days (2.8 years) for ICD and 829 days for CRT (2.3 years), *P* = 0.0004, respectively.

Discussion

Summary of findings

The 5 year survival rates for ICD and CRT were 64% and 58%, respectively, much higher than for non-device patients. Hospital service use before and after cardiac device implantation was predominantly non-HF related, perhaps reflecting the high level of background co-morbidity. Of the HF-related hospital use before and after cardiac device implantation, inpatient admissions were the most common hospital service used, although ED and outpatient presentations were also high. Post-implantation device complication rates were around twice as common in ICD than in CRT patients; the

mean time to replacement was longer for ICD than for CRT in the small minority of patients that required device replacement. Only those with a CRT saw a slight but significant total per-person post-implant cost reduction.

Comparisons with other studies

We previously reported a mortality rate of 38.3% following first emergency admission for HF in England, with half of the surviving patients readmitted to hospital after 1 year.[18] Our current data are similar, with mortality remaining higher than other 1 year estimates from US and continental European hospitals, which ranged from 23.0% to 29.6%.[10,19,20]

We show that those patients who have a cardiac device implanted are, on average, younger (by 5 years for CRT and by 10 years for ICD) and more likely to be male than all patients admitted with HF. This has been reported from the UK audit of device implantation[9] and from other countries.[20,21] Their survival is better than the typical patient who has been hospitalized for the first time with HF, likely due to the high initial post-discharge mortality, with only those who survive this initial high-risk 'vulnerable' period being considered for device therapy, consistent with international guidelines.[7] Additionally, selection of younger people with less co-morbidity for device therapy will ensure a better prognosis than the typical patient admitted to hospital with HF.

Supporting Information, *Table S5* compares the clinical characteristics, and mortality, in the randomized clinical trials of implantable cardiac device therapy with our real-world national administrative data. For CRT therapy, our population was on average 8 years older and had a higher proportion of women than in all but the first RCT of this therapy. Reported co-morbidity was similar for diabetes and underlying coronary artery disease. However, a history of atrial fibrillation (AF) was an exclusion criterion for all trials except MADIT-CRT[12,13] and RAFT,[14] which only included 10–15% such patients. This is in marked contrast to our real-world data that report a coded history of AF in 48% of patients in whom a CRT device was implanted. Additionally, the typical average duration of follow-up was short in the trials

(from 12 months in REVERSE[11] to 40 months in RAFT[14]), although longer-term follow-up was published for three of the trials—albeit after the randomized period had completed.[11,13,22] The reported mortality was highly variable across the trials, reflecting the severity of the HF and the duration of follow-up. Our 5 year all-cause CRT death rate of 41.8% is higher than the corresponding 32% reported from the extension of (non-randomized) follow-up in the CARE-HF trial[22] and 29% in the RAFT trial at the same length of follow-up,[14] presumably reflecting the older age and higher proportion with AF in our patients. We do not have a record of the background medical therapy for the patients in our cohorts, but in the trials, such therapy was excellent and likely better than in usual UK practice at that time. Also using a registry but one merging in administrative data, Boriani *et al.*[23] recruited 1600 consecutive ICD and CRT-D patients and reported 5 year transplant-free mortality rates of 38% and 36%, respectively. They noted a high hospitalization rate, of which co-morbidity was a strong predictor. Using some more recent HES data than us and using a 2015 coding guidance change to try to distinguish between CRT-P and CRT-D, Leyva *et al.*[24] extracted 50 000 CRT patients between 2009 and 2017. Death rates from a 2.7 year median follow-up of 8.2 deaths per 100 person-years for CRT-D and 11.1 for CRT-P extrapolate to 5 year rates of 41.0% and 55.5%, respectively, for a weighted average of approximately 48%; our rate was 42%.

For ICD, patients in our cohort were closer in age to those recruited to the trials (average of 68 years, 5 years younger than typical CRT patients). Perhaps consequently, the sex ratio was similar in our real-world data to that in the trials. The SCD-HeFT trial (median follow-up of 45.5 months) reported a 22% mortality rate in the ICD group, which extrapolates to a 5 year death rate of 29%.[25] The most recent RCT (DANISH) only recruited patients without evidence of underlying ischaemic heart disease and reported a 5 year mortality of only 16% in the ICD arm (21% in the control arm, many of whom also had CRT therapy).[17] Our 5 year all-cause ICD death rate was somewhat higher at 35.9%. This is similar to that reported from the US National Cardiovascular Data Registry's (NCDR) ICD Registry (41.2%).[26] Similar to the CRT trials, the ICD trials enrolled patients who were prescribed excellent medical therapy, likely better than in routine practice, which may also partially explain the difference in mortality between the trial data and our real-world data. The prevalence of a history of AF was substantially higher in our cohort (42%) than in the ICD trials (the highest proportion was 24% in DEFINITE,[16] and such patients were excluded from DANISH[17]).

Our 5 year ICD device complication rate was 13% (with an additional 11% replacement rate), lower than the extrapolated 34% reported from RCTs[27] but much higher than the 3% likely under-reported in an extensive US ICD registry.[24] In contrast, a study using Australian and New Zealand hospitalization data found the average 3 month ICD device complication rate (excluding replacements) to be up to 10%.[28] The

most recently available published UK data report an average re-intervention rate for 'complex device' implants of 6.3% within 12 months,[9] similar to our data.

The main limitation of our study is that the accuracy of secondary diagnosis and procedure fields within HES is lower than for the primary fields and can vary by hospital. Consequently, we were unable to distinguish between CRT-P and CRT-D cardiac implants. In addition, the primary diagnosis field captures the 'main problem treated', which may or may not be the reason for admission. Furthermore, this study included only half of ICD and a third of CRT implantations conducted in England when compared with annual counts from the relevant national registries,[8,29] although our numbers excluded people with existing devices, which represents up to 25% of all UK implants.[9] This discrepancy may introduce an unknown degree of selection bias. We tracked back 5 years before the index date to try to exclude patients with previous implants, but it is possible that this process was not completely effective. Another limitation was that our data, as is common with administrative records, lacked health-related quality of life information.

Policy implications

The debate continues regarding the applicability of real-world observational data on estimating the clinical and cost-effectiveness of therapy, due to concerns around selection bias, coding quality, and missing data. However, RCTs are highly protocol-driven environments where populations are carefully selected and cared for and therefore tend to have a better outcome than less selected patients. Follow-up times are generally short, making extrapolation to longer time periods challenging. Our data, from routine practice, suggest that many of the assumptions used in the modelling that supported NICE's decision to support the use of these therapies for a broad spectrum of patients with HF were correct and that clinicians are using the evidence base (and reimbursement approval) to implant devices where there is a strong likelihood of benefit. The most recent national audit of device implantation in the UK reports that at least 80% of ICDs are compliant with NICE recommendations, and there was a clear surge in ICD and CRT implant activity after the NICE appraisal.[9]

Examining NICE's most recent health technology appraisal of cardiac implantable device,[7] the likely 5 year mortality estimates for a cohort of patients (aged 66 at entry) that was modelled were indeed similar to our real-world ones for both ICD and CRT. The other major assumption in the appraisal was that the median time to device failure (and the need for replacement) was 7.1 years for ICDs, 10.4 years for CRT-P, and 5.8 years for CRT-D, based on analysis of NHS data from the Central Cardiac Audit Database.[6] Our data suggest that many patients will die before they require a device

replacement: within a 5 year period, 36% of ICD patients had died (42% of CRT patients), but only 11% and 5%, respectively, had required a device replacement unrelated to complications.

Finally, the NICE appraisal assumed a device infection rate of 0.8%.[6] Our data are similar: 12 month coded infection rates were 0.9% for CRT and 1.0% for ICD. We clearly show that much of the hospital activity for a wide spectrum of HF patients does not relate to HF. This may lead to an overestimate of the effects of disease management programmes only focusing on HF. The major difference between the real world and the RCTs is the proportion of patient with AF: most clinicians assume that benefit is also found in such patients, despite the low number of such patients enrolled in the RCTs. This is a controversial topic, but data from other countries also suggest that this is the case: in the European Society of Cardiology CRT Survey across Europe, 26% of patients enrolled at the recruiting centres had a history of AF.[25] Further data are required to confirm the likely benefit in this large subgroup.

Conclusions

In summary, real-world evidence from England suggests that those patients who have CRT or ICD therapy implanted are similar to those enrolled in the RCTs, except for a substantially higher prevalence of AF. The mortality and complication rate for these patients is similar to those enrolled in the trials, suggesting that the technology assessments that supported reimbursement in England made reasonable extrapolations from the trial data. Non-HF-related healthcare activity is high in all patients both prior and after implantation.

Conflict of interest

Funding

Ethics

This study complies with the Declaration of Helsinki, and we have approval from the Secretary of State and the Health Research Authority under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to hold confidential data and analyse them for research purposes (CAG ref 15/CAG/0005). We have approval to use them for research and measuring quality of delivery of healthcare, from the London - South East Ethics Committee (REC ref 20/LO/0611).

Supporting information

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

Table A. OPCS procedure codes for index procedures.
Table B. ICD10 codes for adverse events.
Table C. OPCS codes for removal, resiting and renewal (replacement) of device.
Table D. Total inpatient and day case admissions and costs for each group in the 12 months before and the 12 months after the index month (index month not included).
Table E. Total ED visits not ending in admission for each group in the 12 months before and the 12 months after the index month (index month not included).
Table F. Total outpatient department appointment for each group in the 12 months before and the 12 months after the index month (index month not included).
Table G. Comparisons of the study population for key randomised clinical trials of cardiac device implantation in patients with heart failure, compared with real world data from NHS in England, Apr 2011 to Mar 2013.
Figure H. All-cause admissions by type of admission for the non-device patients.
Figure J. All-cause admissions by type of admission for CRT patients.
Figure K. Plot of overall mean cost of admissions by patient group.

Figure L. Plot for OPD costs over time for the three groups.
Figure M. Plot of all admissions split by the primary diagnosis into HF vs non-HF for the no-device group.
Figure N. Plot of all admissions split by the primary diagnosis into HF vs non-HF for the CRT group.
Figure P. Plot of all admissions split by the primary diagnosis

into HF vs non-HF for the ICD group.
Figure Q. Plot for ED visits that do not result in admission.
Figure R. Plot for outpatient department (OPD) appointments over time.

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