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RESEARCH ARTICLE

Cardiac device therapy in patients with left ventricular dysfunction and heart failure: 'real-world' data on long-term outcomes (mortality, hospitalizations, days alive and out of hospital)

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Background The impact on long-term outcomes of implantable cardioverter defibrillators (ICDs) and biventricular defibrillators for cardiac resynchronization (CRT-D) devices in 'real world' patients with heart failure (HF) needs to be assessed in terms of clinical effectiveness.

Methods and results A registry including consecutive HF patients who underwent a first implant of an ICD (891 patients) or a CRT-D device (709 patients) in 2006–2010 was followed (median 1487 days and 1516 days, respectively), collecting administrative data on survival, all-cause hospitalizations, cardiovascular or HF hospitalizations, and days alive and out of hospital (DAOH). Survival free from death/cardiac transplant was 61.9% and 63.8% at 5 years for ICD and CRT-D patients, respectively. Associated comorbidities (Charlson Comorbidity Index) had a significant impact on death/cardiac transplant, as well as on hospitalizations. The median values of DAOH% were 97.4% for ICD and 97.7% for CRT-D patients, but data were highly skewed, with the lower quartile of DAOH% values including values ranging between 0% and 52.8% for ICD and between 0% and 56.1% for CRT-D patients. Charlson Comorbidity Index was a very strong predictor of DAOH%.

Conclusions Patients who were implanted in 'real world' clinical practice with an ICD or a CRT-D device have, on average, a relatively favourable outcome, with a survival of around 62–64% at 5 years, but with an important burden of hospitalizations. Comorbidities, as evaluated by means of the Charlson Comorbidity Index, have a significant impact on outcomes in terms of mortality/heart transplant, hospitalizations and days spent alive and out of hospital.

Keywords Cardiac resynchronization therapy • Defibrillators • Epidemiology • Heart failure • Hospitalizations • Outcome

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Introduction

Implantable cardioverter defibrillators (ICDs) and biventricular defibrillators for cardiac resynchronization therapy (CRT-D) devices are treatments of proven efficacy in appropriately selected patients with left ventricular dysfunction and heart failure (HF).[1–5] Implantable cardioverter defibrillators are targeted to treat ventricular tachyarrhythmias, to prevent sudden death and in patients with left ventricular dysfunction and HF are indicated for either primary or secondary prevention strategies.[6] Cardiac resynchronization therapy is targeted to reduce hospitalizations and improve outcomes and is currently indicated in patients with left bundle branch block or wide QRS, and New York Heart Association (NYHA) class II–III.[5] Devices implanted for CRT can include therapies for ventricular tachyarrhythmias.[4,5] Despite the efficacy proven in randomized controlled trials, there is still uncertainty about how far this is being translated into routine clinical practice where patient characteristics may be significantly different from those seen in trials.[7,8]

The aim of the present study was to analyse the long-term outcome of patients with HF treated with ICD or CRT-D devices, in the context of a single Italian region (Emilia-Romagna), by assessing, with the aid of complete administrative data, survival free from death/cardiac transplant, as well as the overall burden of hospitalizations (evaluating days alive and out of hospital), and the clinical predictors of outcome.

Methods

In July 2005, the Regional Health Care and Social Agency of Emilia-Romagna, an Italian region with around 4.4 million inhabitants, launched a prospective Web-based registry called RERAI (Registry of Emilia Romagna on Arrhythmia Interventions), aimed at collecting clinical and implant data for all cardiac devices implanted in the region.[9,10] All 21 public and four private regional cardiology centres implanting ICDs and CRT devices participated in the collection of data.

In the present study (conceived in accordance with the principles of the most recent revision of the Declaration of Helsinki), we analysed data from all consecutive patients resident in Emilia-Romagna who underwent a first implant of an ICD or a CRT-D device between January 2006 and December 2010, and had a clinical profile at implant characterized by mild to severe HF (NYHA class II–IV) and left ventricular ejection fraction ≤35%. Device replacements and upgrades of a previous implant were excluded from the present analysis. As the RERAI registry was designed to observe current clinical practice, the ethics committees of each participating hospital required only ordinary written informed consent for implant (in line with national regulations) and anonymous publication of scientific data. Written informed consent was obtained from all patients.

In 2010, the regional health-care authority promoted a clinical audit in all cardiology centres, to evaluate the appropriate indication to implant of ICDs and CRT-D devices, according to national and international consensus guidelines and current practice. The results of this audit were encouraging, with 94.5% of implants performed in line with consensus guidelines and current practice, according to consensus of experts. The insertion of an ICD or CRT-D device was classified as primary prevention if performed in a patient identified as a subject at increased risk of sudden cardiac death, in the absence of previously documented sustained ventricular tachyarrhythmia or cardiac arrest. Information on post-implant follow-up was retrieved from the regional database of hospital discharge records and the regional mortality registry. Individuals were linked across data files with anonymous patient identifiers and data were followed for a minimum of 3 years up to a maximum of 8 years. The primary end-point of the present analysis was all-cause mortality/cardiac transplant. The secondary end-points were all-cause hospitalizations, hospitalizations owing to HF, cardiovascular hospitalizations (Major Diagnostic Categories 5, Circulatory System) and percentage of days spent alive and out of hospital.[11] Hospitalization was defined as any hospitalization involving at least one overnight stay since the index hospitalization, including device implantation. Hospital discharge records included administrative data related to date of start and end of any hospitalization, as well as clinical data related to primary and secondary diagnosis. All the events that occurred after a cardiac transplant were not considered in the present analysis.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD) and were compared by the unpaired *t*-test; categorical variables were expressed as counts and percentages and the comparison was performed by the chi-square test.

Age, gender, urgent/planned admission, indications at implantation, patient clinical history, NYHA class, cardiac rhythm, QRS width and Charlson Comorbidity Index (CCI)[12] were compared between ICD and CRT-D patient subgroups. The CCI was used to measure burden of disease and case mix: diagnoses were identified on the basis of ICD-9-CM (International Classification of Disease, 9th edition, Clinical Modification) codes in the index admission and in the previous 2 years.

Cumulative incidence of events at 5 years in the ICD and CRT-D subgroups was estimated by the Kaplan–Meier method: observations were censored at the time of the event (death or heart transplantation) or at the end of follow-up. Further Kaplan–Meier event-free survival models, stratified by NYHA class and CCI, were performed, and survival curves were compared, within the group of patients implanted with ICD and CRT-D devices using the log rank test. Risks of events were evaluated by using a univariate and a multivariable Cox proportional hazard model: the results were reported as hazard ratios (HR) with 95% confidence interval (CI).

A cumulative incidence function, which accounts for the competing risk of mortality, was implemented to estimate all-cause, HF and cardiovascular hospitalizations.

To summarize, the overall impact of ICD or CRT-D implantation on mortality and morbidity, the composite end-point 'Days Alive and Out of Hospital' (DAOH) was calculated. The DAOH were calculated for each patient as follows: days in hospital (length of stay) and days dead (days between death and end of the follow-up time—31 December 2013) were subtracted from total potential follow-up time. The percentage of DAOH was calculated dividing the patient's DAOH by the total potential follow-up time, to reduce the effect of different follow-up times. Finally, a multivariate linear regression model was implemented to evaluate association between DAOH and baseline patient characteristics: the effect of different potential follow-up times was removed by forcing the variable that measures it.

The level of significance was set at 5% ($P < 0.05$) and all statistical analyses were performed using SAS 9.1.3 system (SAS Institute, Cary, NC, USA).

Table 1 Demographic characteristics of patients according to type of implanted device

Patient characteristics	ICD ($n = 891$)	CRT-D ($n = 709$)	P-value
Age (years)			
Mean ± SD	66.5 ± 10.7	67.1 ± 9.7	0.2358
≥65 (%)	64.2	67.3	0.1979
≥75 (%)	23.3	23.3	0.9729
≥80 (%)	8.1	4.1	0.0011
Male gender (%)	84.0	75.5	<0.0001
Indications for device implants			
Primary prevention (%)	82.0	94.9	<0.0001
Secondary prevention (%)	18.0	5.1	<0.0001
Implant during unplanned, urgent hospitalization (%)	36.9	28.2	0.0003
Aetiology and NYHA functional class			
Underlying ischaemic heart disease (%)	66.0	38.6	<0.0001
Non-underlying ischaemic heart disease (%)	34.0	61.4	<0.0001
NYHA functional class II (%)	69.9	27.6	<0.0001
NYHA functional class III (%)	26.5	66.4	<0.0001
NYHA functional class IV (%)	3.6	5.9	0.0273
Rhythm at implant			
Sinus rhythm (%)	79.6	81.4	0.3740
Atrial fibrillation (%)	18.1	14.1	0.0333
Pacemaker rhythm	2.3	4.5	0.0141
QRS width at implant			
QRS width (mean ± SD)	116.8 ± 29.8	150.7 ± 29.0	<0.0001
QRS ≥ 120 ms (%)	47.7	90.6	<0.0001
Charlson Comorbidity Index (mean ± SD)	2.5 ± 1.7	2.4 ± 1.8	0.3189

CCI, Charlson Comorbidity Index; CRT-D, cardiac resynchronization therapy with defibrillation; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.

Results

A total of 2912 patients implanted with a cardiac device in Emilia-Romagna between 1 January 2006 and 31 December 2010. Among these patients, 1312 were excluded because they were in NYHA functional class I (n = 595), had an ejection fraction >35% (n = 658) or had some missing data (n = 59). The final cohort consisted of 1600 patients (891 patients implanted with an ICD and 709 with a CRT-D). Patient characteristics are shown in *Table 1*. As expected, the clinical profiles of patients implanted with an ICD or a CRT-D device were markedly different, with a higher prevalence among ICD patients of indications resulting from secondary prevention of sudden death as well as a higher prevalence of ischaemic aetiology. The prevalence of moderate/severe HF was higher in patients implanted with a CRT-D device, for whom the implant was more frequently done during a planned hospital admission.

Follow-up: occurrence of death/cardiac transplant

For ICD patients the median follow-up was 1487 days (IQ range 1126–1825); for CRT-D patients it was 1516 days (IQ range 1125–1825). The end-point of death/cardiac transplant occurred in 311 patients implanted with an ICD (34.9%) and in 237 patients implanted with a CRT-D (33.4%), including 9 cardiac transplants in the ICD group and 10 in the CRT-D group.

Survival free from death/cardiac transplant was 91.9% at 1 year, 77% at 3 years and 61.9% at 5 years for ICD patients and 91% at 1 year, 76.6% at 3 years and 63.8% at 5 years for CRT-D patients, respectively (*Figure 1*).

The predictors of survival free from death/cardiac transplant at multivariable Cox regression analysis (*Table 2*) were age, device implant during unplanned, urgent hospitalization (as opposed to planned hospitalization), NYHA class III and IV (with NYHA class II as reference) and CCI (as a continuous variable). In CRT-D patients, male gender was also a predictor of mortality/cardiac transplant.

Figure 2 shows the Kaplan–Meier curves of survival free from death/cardiac transplant for ICD and CRT-D patients, respectively, according to NYHA class. Both in ICD and CRT-D patients, the end-point of mortality/cardiac transplant was increased in NYHA class III and class IV (assuming NYHA class II as the reference). For patients implanted with an ICD, the HR for death/cardiac transplant in NYHA class III patients was 1.782 (95% CI 1.406–2.259, $P \leq 0.0001$) and for NYHA class IV it was 2.395 (95% CI 1.476–3.886, $P = 0.0004$). For patients implanted with a CRT-D device, the HR for death/cardiac transplant in NYHA class III patients was 2.412 (95% CI 1.671–3.481, $P \leq 0.0001$) and for NYHA class IV it was 5.263 (95% CI 3.156–8.778, $P \leq 0.0001$).

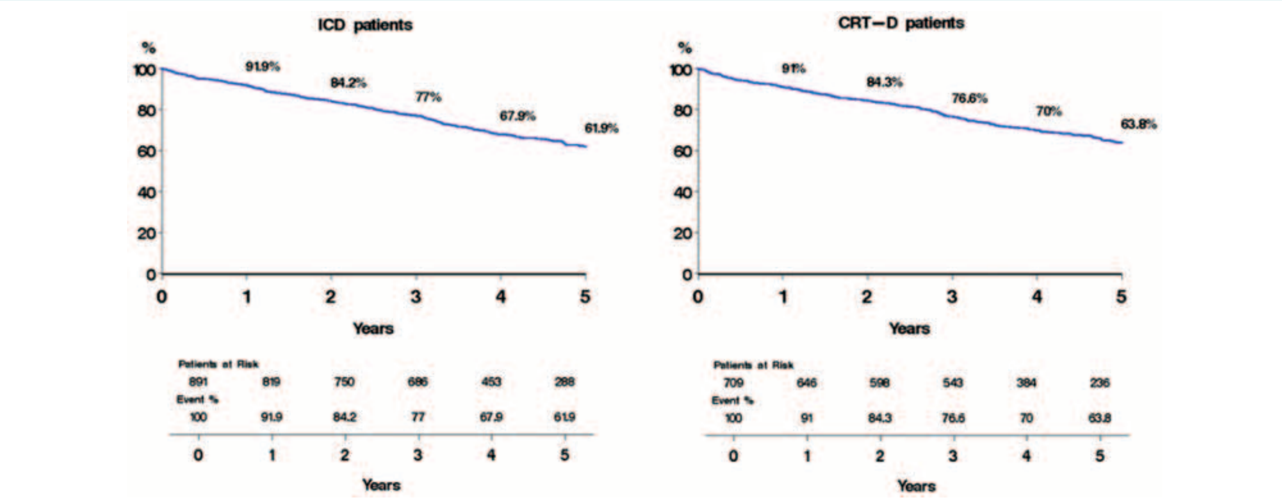

Figure 1 Kaplan–Meier curve of survival free from death/cardiac transplant in patients implanted with an implantable cardioverter defibrillator (ICD; left panel) or a cardiac resynchronization therapy with defibrillation (CRT-D) device (right panel).

Table 2 Predictors of death/cardiac transplant at multivariable Cox regression analysis

	HR	95% CI		Chi-square test
ICD patients				
Age	1.038	1.025	1.050	<0.0001
Unplanned, urgent hospitalization (reference: planned hospitalization)	1.346	1.066	1.699	0.0126
NYHA class III (reference: NYHA class II)	1.574	1.235	2.006	0.0002
NYHA class IV (reference: NYHA class II)	2.597	1.578	4.272	0.0002
CCI	1.228	1.160	1.300	<0.0001
CRT-D patients				
Age	1.023	1.007	1.040	0.0058
Male gender	1.411	1.008	1.975	0.0449
Unplanned, urgent hospitalization (reference: planned hospitalization)	2.007	1.539	2.617	<0.0001
NYHA class III (reference: NYHA class II)	1.775	1.222	2.579	0.0026
NYHA class IV (reference: NYHA class II)	2.864	1.690	4.856	<0.0001
CCI	1.182	1.110	1.258	<0.0001

CCI, Charlson Comorbidity Index; CRT-D, cardiac resynchronization therapy with defibrillation; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.

Figure 3 shows the Kaplan–Meier curves of survival free from death/cardiac transplant for ICD and CRT-D patients, respectively, according to CCI. Both in ICD and CRT-D patients, the end-point of mortality/cardiac transplant was increased in the case of a higher burden of comorbidities. In this analysis, the populations were analysed according to distribution in tertiles of this comorbidity index (0–1 CCI, 2–3 CCI, 4–11 CCI) and the lower tertile of CCI was assumed as the reference. For patients implanted with an ICD, assuming a 0–1 CCI as the reference, the HR for death/cardiac transplant in patients with a 2–3 CCI was 1.184 (95% CI 0.889–1.577, $P = 0.2470$), and for patients with a 4–11 CCI the HR was 2.649 (95% CI 1.997–3.516, $P \leq 0.0001$). For patients implanted with a CRT-D device, the HR for death/cardiac transplant in patients with a 2–3 CCI was 1.404 (95% CI 1.018–1.938, $P = 0.0388$) and for patients with a 4–11 CCI the HR was 2.943 (95% CI 2.146–4.035, $p \leq 0.0001$).

Follow-up: occurrence of hospitalizations

During the follow-up among the 891 ICD patients, 148 (16.6%) had no new hospitalizations following device implant (rehospitalizations for any cause), while the others had a median of 3 (mean 4.0) hospitalizations for any cause (range 0–60). Among the 709 CRT-D patients, 126 (17.8%) had no rehospitalizations (for any cause), while the others had a median of 3 (mean 3.8) hospitalizations for any cause (range 0–27). Taking into account the patients with rehospitalizations, the hospitalizations were for cardiovascular reasons in 612 (82.4%) patients implanted with an ICD and in 470 (80.6%) patients implanted with a CRT-D device.

In the Supplementary material online, *Figure S1* shows the survival free from all-cause hospitalizations (panel A, top), cardiovascular hospitalization (panel B, mid) and hospitalization for HF (panel C, bottom) for ICD and CRT-D patients, respectively. *Tables 3* and *4* show the predictors of all the above-mentioned types of hospitalization at multivariable Cox regression analysis, for patients implanted with an ICD and a CRT-D device, respectively.

Follow-up: days alive and out of hospital

Days alive and out of hospital were analysed according to administrative data, and *Figure 4* shows the percentage distribution of DAOH during follow-up with regard to patients implanted with an ICD and a CRT-D device, respectively. The range of distribution was extremely wide, from 0 to 100%, with mean values and

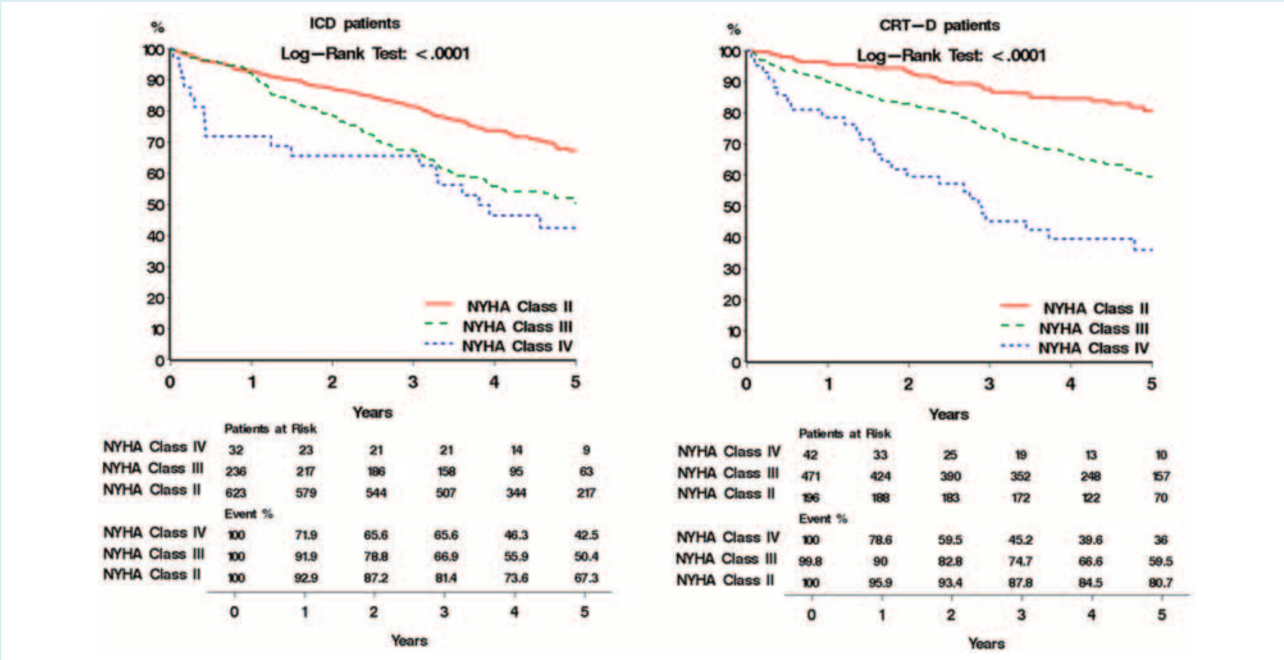

Figure 2 Kaplan–Meier curves of survival free from death/cardiac transplant according to New York Heart Association (NYHA) class in patients implanted with an implantable cardioverter defibrillator (ICD; left panel) or a cardiac resynchronization therapy with defibrillation (CRT-D) device (right panel).

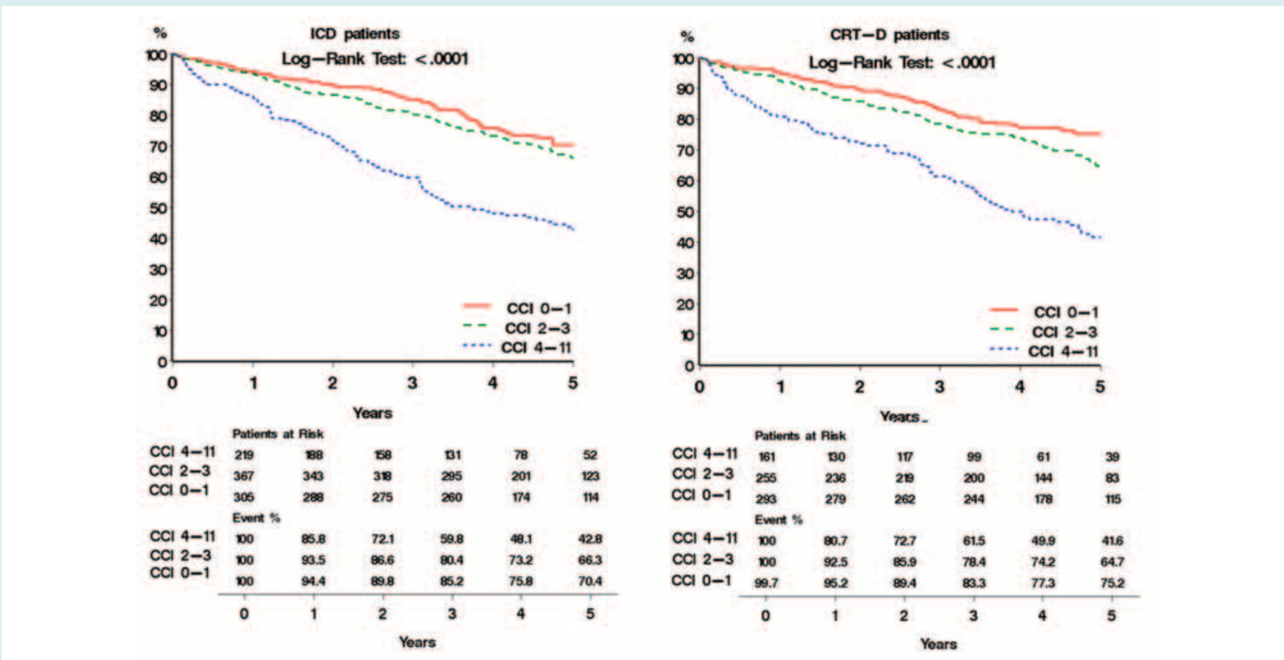

Figure 3 Kaplan–Meier curves of survival free from death/cardiac transplant according to Charlson Comorbidity Index (CCI) in patients implanted with an implantable cardioverter defibrillator (ICD; left panel) or a cardiac resynchronization therapy with defibrillation (CRT-D) device (right panel).

Table 3 Predictors of all-cause hospitalizations, cardiovascular hospitalizations and heart failure hospitalizations for implantable cardioverter defibrillator (ICD) patients

	HR	95% CI		Chi-square test
All-cause hospitalizations				
Age	1.019	1.011	1.026	<0.0001
Implant during unplanned, urgent hospitalization (reference: planned hospitalization)	1.449	1.245	1.686	<0.0001
NYHA class III (reference: NYHA class II)	1.372	1.165	1.616	0.0002
NYHA class IV (reference: NYHA class II)	1.982	1.339	2.932	0.0006
CCI 2–3 (reference: CCI 0–1)	1.135	0.956	1.349	0.1484
CCI 4–11 (reference: CCI 0–1)	1.654	1.360	2.011	<0.0001
Cardiovascular hospitalizations				
Male	0.761	0.599	0.968	0.0260
Implant during unplanned, urgent hospitalization (reference: planned hospitalization)	1.425	1.179	1.724	0.0003
NYHA class III (reference: NYHA class II)	1.279	1.035	1.580	0.0226
NYHA class IV (reference: NYHA class II)	2.577	1.679	3.953	<0.0001
CCI 2–3 (reference: CCI 0–1)	1.305	1.049	1.623	0.0168
CCI 4–11 (reference: CCI 0–1)	1.416	1.102	1.820	0.0066
Heart failure hospitalizations				
NYHA class III (reference: NYHA class II)	1.580	1.188	2.101	0.0017
NYHA class IV (reference: NYHA class II)	1.455	0.713	2.969	0.3023

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.
Tertiles of CCI: 0–1 CCI, 2–3 CCI, 4–11 CCI.

interquartile ranges shown at the top of *Figure 4*. The median values of DAOH were 97.4% for ICD and 97.7% for CRT-D patients, but data were highly skewed, with the lower quartile of DAOH% including values between 0% and 52.8% for ICD and between 0% and 56.1% for CRT-D patients.

Table 5 shows the results of multivariable stepwise linear regression. For patients implanted with an ICD, the amount of DAOH was negatively affected by age, device implantation during urgent, unplanned hospitalization, NYHA classes III and IV, as well as high (4–11) CCI. For patients implanted with a CRT-D device, a significant reduction of DAOH was found for male gender, urgent, unplanned hospitalization, NYHA class III and IV, as well as high (4–11) CCI. The only variable associated with a significant increase in DAOH was device implantation in the setting of primary prevention, but this was observed only for ICD patients. It is noteworthy that the CCI was a very strong determinant of DAOH as the corresponding values of parameter estimate (*Table 5*) were a major determinant of DAOH, after NYHA functional class IV.

Discussion

Treatment with ICD and CRT-D devices has specific indications, validated by randomized clinical trials in terms of efficacy and

Table 4 Predictors of all-cause hospitalizations, cardiovascular hospitalizations and heart failure hospitalizations for cardiac resynchronization therapy with defibrillation (CRT-D) patients

	HR	95% CI		Chi-square test
All-cause hospitalizations				
Implant during unplanned, urgent hospitalization (reference: planned hospitalization)	1.740	1.447	2.091	<0.0001
NYHA class III (reference: NYHA class II)	1.144	0.940	1.392	0.1801
NYHA class IV (reference: NYHA class II)	1.770	1.228	2.552	0.0022
Atrial fibrillation (reference: non-atrial fibrillation rhythm)	1.360	1.079	1.715	0.0093
CCI 2–3 (reference: CCI 0–1)	1.250	1.031	1.515	0.0230
CCI 4–11 (reference: CCI 0–1)	1.625	1.308	2.019	<.0001
Cardiovascular hospitalizations				
Age	0.988	0.977	0.998	0.0248
Implant during unplanned, urgent hospitalization (reference: planned hospitalization)	1.821	1.451	2.284	<.0001
Non-ischaemic heart disease (reference: ischaemic heart disease)	0.724	0.583	0.898	0.0033
Heart failure hospitalizations				
Implant during unplanned, urgent hospitalization (reference: planned hospitalization)	1.868	1.340	2.604	0.0002
CCI 2–3 (reference: CCI 0–1)	1.514	1.040	2.204	0.0306
CCI 4–11 (reference: CCI 0–1)	1.762	1.161	2.672	0.0078

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

with acceptable cost-effectiveness[2,13–15] Use of registries has been advocated in order to evaluate 'real world' effectiveness, in less 'selected' populations compared with randomized trials, even if registries have recognized limitations mainly because of internal validity (selection bias) and missing data.[16] In the present study, we evaluated patient outcomes at a 4-year median follow-up in two cohorts of patients implanted with an ICD or a CRT-D device. It is notable that the CRT-D follow-up data reported in the present study cover a longer follow-up period than those of all the randomized studies performed so far and an even longer period than those of some multicentre registries such as the European CRT Survey (1-year follow-up)[17] or the National Cardiovascular Data Registry's ICD Registry (3-year follow-up).[18]

The present study shows that patients implanted in 'real world' clinical practice have, on average, a relatively favourable outcome, with survival of around 62–64% at 5 years. Moreover, the outcome of patients implanted with an ICD or a CRT-D device can be predicted by a series of variables including patient characteristics (age, NYHA class, CCI) and the admission setting (device implantation during urgent unplanned vs. planned hospitalization). The latter is an interesting finding, previously reported for CRT-D,[19] that indicates the prognostic implications of patient clinical instability. Recently, in a large cohort of elderly Medicare and Medicaid patients, including patients implanted with a prophylactic ICD and non-implanted patients (with propensity score adjustment), no

	N° patients	DAOH Minimum	DAOH Mean	DAOH Median	DAOH 25th percentile	DAOH 75th percentile	DAOH Maximum
ICD	891	0	77.1	97.4	52.8	99.2	100
CRT-D	709	0	77.6	97.7	56.1	99.3	100

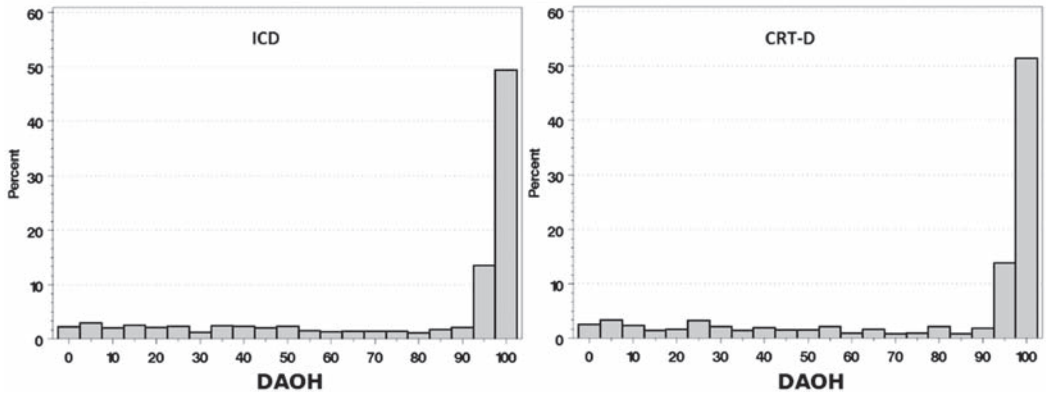

Figure 4 Percent distribution of days alive and out of hospital (DAOH) during post-implant follow-up. ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy with defibrillation.

Table 5 Multivariable stepwise linear regression analysis for predicting days alive and out of hospital (DAOH) in patients implanted with an implantable cardioverter defibrillator (ICD) or a cardiac resynchronization therapy with defibrillation (CRT-D) device, respectively

	Parameter estimate	Standard error	P-value
ICD patients			
Total follow-up time	0.61030	0.04164	<0.0001
Age	−10.48169	1.98818	<0.0001
Primary prevention (reference: secondary prevention)	131.31663	58.08820	0.0240
Implant during unplanned, urgent hospitalization (reference: planned hospitalization)	−115.26299	45.47068	0.0114
NYHA class III (reference: NYHA class II)	−199.03198	47.30061	<0.0001
NYHA class IV (reference: NYHA class II)	−419.43194	113.11492	0.0002
CCI 4–11 (reference: CCI 0–1)	−321.22874	48.37016	<0.0001
CRT-D patients			
Total follow-up time	0.57783	0.04698	<0.0001
Male	−123.76685	56.10300	0.0277
Implant during unplanned, urgent hospitalization (reference: planned hospitalization)	−344.57344	54.10478	<0.0001
NYHA class III (reference: NYHA class II)	−151.36271	55.13822	0.0062
NYHA class IV (reference: NYHA class II)	−445.37770	110.89928	<0.0001
CCI 4–11 (reference: CCI 0–1)	−321.31620	58.21050	<0.0001

CCI, Charlson Comorbidity Index; NYHA, New York Heart Association.

benefit emerged when the implant was inserted during a hospital admission for exacerbation of HF or other acute comorbidities.[20] Obviously, in daily practice, patients should be stabilized before being implanted, but in some cases stabilization is not possible and, according to our data, this condition identifies subgroups of patients at higher risk.

Another interesting point suggested by our data is the great impact of comorbidities on outcomes, as not only mortality and heart transplantation but also all-cause hospitalizations were related to device implantation during urgent, unplanned hospitalization. As diagnoses other than HF are the main reason for most hospitalizations (i.e. pulmonary disease, renal failure, gastrointestinal diseases, etc.) in HF patients, this is a good argument for analysing hospitalizations for any cause in studies exploring the ‘real world’.[21]

Our approach, based on clinical and administrative databases, made it possible to assess the global burden of hospitalization during follow-up, combining data on vital status with DAOH evaluation, a new measurement proposed for summarizing the overall absolute treatment effect on mortality and morbidity.[11] This approach appears to be much more comprehensive in comparison with the traditional outcome hospitalizations (i.e. ‘time to first hospitalization’),[22–24] thus offering the advantage of providing information of value from different perspectives (patients, payers, and the health care system).[25,26] Although DAOH varied widely (from 0 to 100%) in our study, the median value was around 97% for both ICD and CRT-D patients. However, further studies should be devoted to identifying and potentially predicting those patients belonging to the lower quartile of DAOH who, in our cohort, experienced a quota of DAOH between 0% and around 53–56% of the follow-up period. As previously argued,[11] DAOH, in particular DAOH%, may provide a valuable tool for summarizing the overall absolute effect of a treatment on mortality and morbidity, although few data are available in the literature.[11,27,28] With regard to patients implanted with an ICD or a CRT-D, the effect on DAOH has never been reported by registries or trials with extended follow-up: it appears useful to characterize patients with the lower values of DAOH either for improved patient targeting with regard to device implantation or for implementing more sophisticated forms of care delivery, such as disease management with remote monitoring.[29–31]

The assessment of the burden of all-cause hospitalizations is not an easy task to distinguish in observational studies with long follow-up and, in this perspective, the use of administrative data even to measure the DAOH%, as done in this study, could be considered an important tool for having a full picture of all the hospitalizations.[32–35] A previous study, based on analysis of administrative datasets, was focused on the value of this type of approach in the specific setting of use of ICDs in the real world.[34]

Our data indicate that male gender has negative prognostic implications in patients treated with CRT-D confirming, in a 'real world' setting, the findings derived from observational and controlled studies or meta-analyses.[36–38]

Finally, the present study shows that survival and all-cause/HF hospitalizations are worse when the burden of comorbidities is high. Comorbidities are included in all the prognostic scores validated for HF,[4] as well as in the CCI that we adopted, according to the literature.[12,32,33,39,40] While CCI has been shown to correlate with mortality within 1 year after ICD insertion,[40] no previous data have highlighted its role in predicting DAOH%. It is notable that upon multivariable stepwise linear regression analysis for prediction of DAOH (*Table 5*), a high CCI achieved a very powerful effect on DAOH after NYHA class IV, thus indicating how important and pronounced the effect of comorbidities is on DAOH. It is still an open question whether remote monitoring can also have a positive impact on management of comorbidities from the perspective of full-spectrum disease management.[29–31]

Limitations

The characteristics and the observational nature of the present study do not allow comparison of the outcome in patients implanted with an ICD with the outcome of patients implanted with a CRT-D device. For indications of whether to implant an ICD or a CRT-D device, centres followed consensus guidelines and current practice and, in this regard, an audit of a sample of implanted devices performed during the study period in this region showed very good compliance with consensus guidelines across the region with regard to indications and concurrent pharmacological treatments.

The indications to implant a device included in consensus guidelines have changed with time and therefore there are limitations in generalizing our findings to patients implanted according to most recent recommendations.[5]

In the present study we did not assess response to CRT-D or shocks delivered by the defibrillator function; this is, however, in line with the general role of registries, devoted to assessing outcomes rather than response to therapies.[16] Moreover, we did not consider patients implanted with a pacemaker for cardiac resynchronization therapy (CRT-P devices) because insertion of a CRT-D device accounts for 84–90% of implants performed in our region in patients with indications for cardiac resynchronization therapy.[10] In the literature, the use of CRT-P devices was associated with reduced mortality, owing to fewer deaths both from worsening HF and sudden death.[41]

Conclusions

The present study indicates that patients implanted in 'real world' clinical practice with an ICD or a CRT-D device have, on average, a relatively favourable outcome, with survival of around 62–64% at 5 years. However, there is an important burden of cardiovascular and non-cardiovascular hospitalizations, that constitute both an organizational and financial challenge for health-care systems.[25] Comorbidities have a significant effect on outcomes, both in terms of mortality/heart transplant and hospitalizations, and are one of the key determinants of the number of days spent alive and out of hospital. The DAOH variable should be more extensively investigated in future studies focused on interventional and device therapies, as assessment and monitoring could improve patient targeting, which is the cornerstone of any economic evaluation based on cost-effectiveness and cost-utility.[13–15,25] With adequate support from health authorities, DAOH could be calculated from administrative datasets, with full coverage of long follow-up periods, thus extending the value and the impact of outcome research.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Kaplan–Meier curves of survival free from all-cause hospitalizations (panel A, top), cardiovascular hospitalization (panel B, mid) and hospitalization for HF (panel C, bottom) for ICD and CRT-D patients, respectively.

Appendix S1. RERAI investigators.

Conflicts of interest: G.B. reports small personal fees from Boston, Medtronic (small amount), and from Boehringer, outside the submitted work. E.DM. reports personal fees from Speaker Honoraria from Boston Scientific, and personal fees from Proctorship agreement with Boston Scientific for training health-care professionals on Subcutaneous Implantable Defibrillator (S-ICD) procedure, outside the submitted work. C.T. reports personal fees from Boston Scientific Italia and personal fees from Biotronik Italia outside the submitted work. M.Z. reports personal fees and non-financial support from St Jude Medical, and personal fees and non-financial support from Medtronic, outside the submitted work. No conflict of interest declared for the other authors.

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